PROCEEDINGS
OF
THE EIGHTH U.S.-JAPAN WORKSHOP
ON GLOBAL CHANGE

HEALTH AND THE ENVIRONMENT: CLIMATE CHANGE AND THE HEALTH EFFECTS OF EXPOSURE TO ULTRAVIOLET RADIATION AND EXPOSURES TO HIGHER TEMPERATURES AND AIR POLLUTANT CONCENTRATIONS

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Joint Report

U.S.-Japan Workshop on Global Change
Report of the Co-Convenors

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The 8th US-Japan Workshop on the Impacts of Global Change on Human Health was divided into two major themes. In the first, global change scenarios developed by the Intergovernmental Panel on Climate Change (IPCC) were used to guide the development of research recommendations. These scenarios project an increase in surface temperatures of 2-5°C in the next 50 to 100 years. As a result of these temperature changes, a greater frequency of longer lasting heat waves are also projected for warmer summer months. Temperature changes of this magnitude appear to be linked to increasing atmospheric concentrations of CO_2. A primary source of increasing CO_2 concentrations is the combustion of fossil fuels. Therefore, along with greater and more long lasting exposures to higher temperatures, especially for people who live in urban areas, there could also be greater and more long lasting exposures to concentrations of air pollutants. As a result, another impact of global change on human health is an increase in morbidity and mortality for those diseases related to exposures to both higher temperatures and concentrations of air pollutants.

For the second theme of the 8th Workshop, depletion of stratospheric ozone is presently occurring to the greatest extent over the polar regions on our planet. In the next 25 to 50 years, however, there could be significant depletion of stratospheric ozone over temperate and equatorial latitudes where most of the world's populations live. In these latitudes, depletion of stratospheric ozone may result in greater exposures to shorter wavelength UV radiation (UV-A and UV-B) and may result in increases in rates of skin cancers, ocular diseases and diseases associated with compromised cutaneous and systemic immune systems.

In assessing the impacts of these global changes, the 8th US-Japan Workshop has placed greater emphasis on multi-disciplinary, multi-national, integrated research activities that could provide quantitative estimates of the impacts of global change on human health. Such comprehensive research approaches are required because exposures to some or all of these environmental agents occur simultaneously. In addition, how these exposures effect the health status of individual members of diverse human populations is an important goal of not only the United State and Japan, but of all nations.

In our deliberations, several important questions guided the discussions for developing research proposals to assess the impacts of global change on human health. These questions include the following. What basic data do we need and how do we put them together in order to make near-term and long-term human health impacts assessments? How will the body respond to increasing temperatures, air pollutant concentrations and

greater exposures to UV radiation? How will we account for the large variability of responses that will be observed in diverse human populations as a result of these exposures? How can we quantify differences in response for the same exposures and relate these responses to individual genetic characteristics, age, pre-existing disease conditions and gender?

Can models be developed to describe cardio-pulmonary, thermal-regulatory system interactions for diverse human populations? Can these models describe how these systems will respond and/or fail as a result of exposures to environmental agents and cause disease? What types of research on molecular mechanisms of asthma, other chronic obstructive pulmonary diseases and cardiovascular diseases would be necessary to estimate the impacts of global change? Can models describe how greater exposures to UV radiation cause skin cancers and ocular diseases? Can models simulate immune system dysfunction that may be important in the development of melanoma and non-melanoma skin cancers and cause individuals to be more susceptibility to infectious diseases?

Finally, the 8th Workshop was indeed fortunate to bring together such a high level of talent and expertise in so many different disciplines from both the United States and Japan to discuss what needs to be done to assess the impacts of global change on human health. Along with descriptions of the types of research that were needed, there were programmatic discussions about the human and financial resources that would be required. Agencies were identified that would need to work together to provide the necessary human and financial resources because these are programs that will cut across programmatic responsibilities of many agencies. These discussions on programmatic issues were an important component of the 8th Workshop because the resources of many agencies in the United States, Japan, and worldwide will be required to implement this complex set of research recommendations.

Section II

Report of Session 1 Co-Chairs
Health Effects of Exposure to Higher Temperatures and Air Pollutants

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Introduction

The Working Groups related to air pollution and global environmental change were each made up of scientists from a wide set of disciplines representing both governmental and non-governmental organizations from the United States and Japan. The disciplines represented included air engineers, atmospheric scientists, epidemiologists, meteorologists, risk assessment modelers, occupational medicine specialists, physiologists, respiratory disease specialists, toxicologists, as well as several research administrators representing several agencies, charged with the responsibility of setting research agendas related to global climate change. Each Working Group meeting had members representing several disciplines and the meetings were organized such that each participant was able to contribute to more than one Working Group.

Several overarching themes and conclusions were reached. There was uniform agreement that in spite of the relative long time frame for global environmental change, there is a great need for a research agenda at this time. Because predicting future impact is difficult at best, advantage should be taken of the existing, albeit episodic, incidents of significant temperature fluctuations to explore at least acute effects of environmental change. In addition, where it is possible to use existing recorded data or data were being collected for other purposes, these data be explored more fully to assess potential interactions of temperature change in association of specific pollutant levels.

Major Recommendations

Each of the Working Groups formulated specific sets of research agenda plans that are discussed within each Working Group summary. Highlights from each group are summarized here. One point of major concern was that there is substantial research in each of the above named disciplines that is being carried out that might be better integrated to attack problems related to the interaction of air pollutants and global change. To provide better access to and to draw upon the expertise that may already exist in each of our countries, it was recommended that review papers be commissioned and workshops specifically designed to present scientific findings be undertaken. In addition, it was recommended that Internet based “chat rooms” could be established under the auspices of the lead U.S. and Japanese agencies to facilitate communication on developing research agendas.

The following recommendations are considered in detail in each Working group report.

1. Studies of personal, indoor and outdoor concentrations of particles and ozone along with activity pattern data bases need to be linked to aircraft measurements to develop models capable of estimating exposure for large populations.
2. Similar studies linking satellite measurements of UV exposure need to be carried out in both countries taking account of differences in housing stocks, activity patterns, and other personal behavior characteristics.
3. Link transboundry studies of ozone-aerosols using aircraft and ozonesonde measurements with data on air quality and health effects to determine relationships between large-scale pollution transport and population-level exposures.
4. Using already collected data starting in the mid-1970's effects of temperature interacting with pollutants on mortality needs to be assessed across a spectrum of cities with different housing, climate and population characteristics.
5. Interagency initiatives should fund analytic prospective epidemiological studies of the health effects of temperature and temperature/air pollution interactions, taking advantage of naturally occurring events.
6. Animal and in vitro studies of effects of heat and humidity interacting with air pollutants need to be conducted in controlled exposure settings.
7. Similar controlled exposure studies need to be conducted in humans taking into account potential susceptibility factors such as normal physiology, age, gender, ethnicity, and presence or absence of cardio-pulmonary diseases.
8. Studies of the effect of adaptation and mechanisms and factors where by it occurs need to be assessed.
9. Develop models using existing and developing data from US-Japan data sources to model effects of technology transfer interacting with environmental change.

Conclusions

Overriding the research agendas proposed by each working group was the concern that more integrated efforts need to be facilitated across disciplines and within each country as well as across countries. The development of research agenda oriented "chat rooms", as mention above would facilitate the latter; however, for the former more integrated research and training are necessary.

To accomplish this aim would require substantial investment in infrastructure directed to carrying out interdisciplinary research and training that incorporates and can be facilitated by developing Centers of Excellence in Global Environmental Health Effects. These centers should be established in university settings and need to link expertise in a wide variety of disciplines. The programs might be oriented toward physiologic and toxicological programs, or epidemiological programs or risk assessment programs. In each case, multidisciplinary (as well as potentially cross-national) representation would be a necessary requirement to establish one of these centers. The nature of the research objective indicated in the research summaries of each of the working groups suggests the kinds of disciplines that might be included in each of these centers. These centers would provide the infrastructure and support for students who would become the future leaders in the field. At a cost of approximately $1-2 million/year this would include support for

research and training for fellowship training slots for both pre- and postdoctoral positions. The importance of such programs would be to begin to provide a forum for the kinds of interdisciplinary research necessary. These data could then be used for developing appropriate complex system modeling and risk assessment parameters to make predictions that will be useful for developing appropriate strategies. These strategies would be effective not only in identifying risks in the developed nations such as the United States and Japan, but also in identifying preventative strategies that may be more appropriately used in the developing world.

Working Group 1: Exposure Monitoring and Modeling

Co-chairs: Y. Matsumoto (NIES) and L. Wallace (EPA)
Participants: M. Kabuto, M. Ando, K. Hirokane (NIES); S. Inoue (National Institute of Agro-environmental Sciences); T. Creech, (NCDC); A. Thompson and N. Maynard (NASA).

Scientific Issues
Working Group 1 looked at two issues. The first was personal exposure to pollutants in the context of global change. The second concerned aspects of pollution—affecting primarily ozone, CO, and aerosols—that are already measured in national and global air quality networks and also in aircraft or from satellites (e.g., the TOMS satellite measurements of tropospheric ozone, aerosols, and UV).

The exposure monitoring group identified four types of monitoring: atmospheric, such as the satellite and aircraft monitoring undertaken by NASA and NOAA; tropospheric, such as the ambient monitoring stations operated by the Japanese and US environmental agencies; and indoor and personal monitoring, normally undertaken only in special studies. We consider monitoring of personal exposure to be the "ground truth" that should ideally be considered in all estimates of exposure to environmental pollution.

Ozone and aerosols (fine particles) are considered to be two of the most important pollutants associated with global warming. Several major studies of personal exposure to particles are presently under way in the United States and Japan. The U.S. studies include personal, indoor, and outdoor residential measurements on subsets of high-risk subpopulations—persons with chronic obstructive pulmonary disease (COPD) and cardiovascular problems. Such studies have been identified as of high priority by the National Academy of Sciences. Japan also plans personal, indoor and outdoor measurements in several cities. As personal exposure depends strongly on human activity pattern, studies should be carried out on various subpopulations in the two countries.

Although personal monitors for fine and inhalable particulates have been developed and validated, they are presently limited to 12-hour or 24-hour integrated samples. A personal monitor for continuous (real-time) measurement of particle mass would be of interest to develop. In the meantime, monitors exist for continuous measurement of particle numbers (using optical scattering) and have been employed successfully in some studies. These should be further studied for their applicability to aerosols of different sources and characteristics (density, morphology, etc.).

Ozone personal monitors are also presently limited to integrated (12-h to 24-h) measures. Because health effects of ozone are expected to be short-term, a nearly continuous monitor for ozone would also be of interest to develop. On the other hand, since few sources of ozone exist inside the home, it may be sufficient to employ indoor and outdoor

continuous monitors to estimate personal exposure, using the ozone badges to validate the estimates.

We believe that the particle and ozone studies should be undertaken concurrently, since the ozone badge can be worn together with the bulkier particle monitor. It will also be important to link such personal exposure studies with existing data on aerosols and ozone from the atmospheric and tropospheric studies of NASA, NOAA, and the Japanese and US environmental agencies mentioned earlier. (contacts: Wallace, Herman, Matsumoto; also Jon Samet, Johns Hopkins).

Exposures to ultraviolet radiation (UVA and UVB) are also important to measure directly. We note the work of Dr. M. Ono in using personal monitors for UVA and believe that a large population-based study, covering the North-South range in the two countries, will be feasible and desirable in the near future. Some further improvement of the UV monitor to allow hourly estimates may be possible. The measurements should be linked with the TOMS satellite estimates of UVA and UVB now available and with the NHAPS estimates of time spent outdoors for the US population. (contacts: Ono, Herman).

Climatic effects of global warming are myriad. Besides increased temperature levels and major variations in precipitation, the amount of cloudiness, convection patterns, winds, and height of the mixing layer will affect air quality. This was illustrated using examples of ozone profiles over the southeast United States and over southern Africa where agricultural and residential burning combine to give very high ambient aerosol concentrations. Also, examples from the extreme Indonesian fires in 1997 (a consequence of the El Nino drought) showed that meteorological patterns are the key to determining pollution exposure. Depending on characteristics of the mixing layer, particulate settling patterns and chemical and UV effects of smoke, ozone and particles may have a different history and lead to different exposures and health effects.

Transboundary pollution and intercontinental transport have emerged as major atmospheric chemical issues on a global scale. This means, for example, the countries or regions upwind may control pllution downwind. An upcoming U.S.-Japanese experiment sponsored by NASA, NSF and NOAA on the U.S. side will be looking at Asian pollution from China and beyond flowing over Japan and toward North America in campaigns in Spring, 2001.

Global warming will result in lengthening of the pollen season and concomitant increase in allergic reactions. Evidence was presented that a 4.4 C rise in temperature expected over the next century would result in a 45-day lengthening of the pollen season in Japan. House dust mites are also expected to extend their range northward. Presently monitors for bioaerosols are limited and considerable research and development will be required to develop monitors capable of providing accurate measures of bacteria, fungi, and allergens. (Contact: Inoue, Takahashi).

Data and Modeling Issues

The ozone/aerosol monitoring undertaken by aircraft and satellites present many opportunities for research partnerships. Some U.S.-Japanese research efforts are already ongoing, including studies of Indonesian fires and vertical ozone profiles in the two countries. SHADOZ is a project that includes 10 stations in the southern hemisphere and will provide ozone profile data for researchers in a number of countries. (contact: Thompson).

Climate/meteorology data are maintained by the National Climate Data Center (Asheville, NC). Historical archives are widely available on the Web from NCDC. Forecasting is carried out by NOAA both short- (CPC) and long-range (NCEP). (contact: Creech).

Transboundary pollution transport and atmospheric chemistry studies will be extremely important in order to understand the effects of global change. Therefore the NASA aircraft and satellite studies and the NCDC climate/meteorological data together with the NOAA modeling capabilities will need to be linked, together with the data from their Japanese counterparts, to obtain better understanding of trans-Pacific movement of aerosols and other pollutants.

Programmatic Considerations

Because of the interdisciplinary nature of these studies, it is often difficult to find a single Agency that will take responsibility for carrying out these studies. We see a need for workshops to identify ways in which several agencies can work together to fund studies that might not otherwise be funded.

The particle-ozone studies of personal exposure would be appropriately carried out by the environmental agencies in the United States and Japan. The cost of these studies is estimated at 1-2 million dollars per year for 3 years.

Since EPA has no regulatory authority for UV, it is unclear whether the UV personal exposure study described above would be undertaken by EPA. The cost would be in the neighborhood of 1 million dollars per year for 3 years. The improvement of the UV monitor would be appropriately carried out in Japan and could be done for relatively small cost.

Development of improved bioaerosol monitors would probably best be undertaken by a series of investigator-initiated projects dealing with specific classes (bacteria, fungi, etc.). These could be relatively small projects, but there would be a number of them, stretching over a number of years as new abilities to speciate come on line.

Recommendations for Japan-U.S. Collaboration

1. Carry out studies of personal, indoor, and outdoor concentrations of particles and ozone. Link with aircraft measurements (NASA) and with activity pattern data bases (NHAPS) to develop models capable of estimating exposure for large populations. Contacts: Wallace, Herman, Matsumoto

2. Carry out similar studies of exposure to UV in both countries. Link with satellite measurements of UV (TOMS program, NASA) and activity pattern data bases to estimate exposures for larger populations.
   Contacts: Ono, Herman

3. Link transboundary (trans-Pacific) studies of ozone-aerosols using aircraft and ozonesonde measurements with data on air quality and health effects to determine relationships between large-scale pollution transport and population-level exposures. Develop vertical temperature profiles and ancillary data to allow better estimation of mixing heights for prediction of pollutant concentrations.
   Contacts: Anne Thompson

4. Encourage studies on monitoring and modelings for both indoor and outdoor bioaerosols.
   Contacts: Harriet Burge, Harvard School of Public Health

Working Group 2: Epidemiological Evidence and Methods of Analysis for Temperature and Air Pollution Induced Disease

Co-chairs: Yasushi Honda, Douglas Dockery
Participants: Mary Gant, Hideo Harasawa, Seishiro Hirano, Petra Koken, Jerry Last, Frank Speizer, Yuichi Takahashi, George Thurston (Rapparteur), Iwao Uchiyama, James Ultman

Scientific Issues
Susceptible Populations: The burden of the effects of temperature and air pollution stresses (extremes) falls unequally on the population. The inability to respond can be defined by multiple dimensions:

- Reduced physiologic response: Inability to maintain homeostasis in response to environmental stress. Groups with reduced reserves and inadequate compensatory mechanisms include the elderly and infants.

- Inadequate behavioral or structural adaptation response: Inability to control one's own environment. For example, economically disadvantaged, homeless, fixed income elderly. Inner city and underserved populations likely to be at higher risk because of higher urban temperatures.

- Health care and societal response: Reduced capacity to obtain medical care or support services. Inadequate insurance, dependence on emergency departments, lack of community support and connections.

Estimation of Changes in Life-Expectancy: How much does temperature events change population life expectancy? Are effects limited to elderly? How much are infant and child mortality affected? How do temperature and air pollution events affect quality of life?

Extreme Weather and Air Pollution Events: There is substantial under-ascertainment of mortality and morbidity associated with extreme temperature and air pollution events. For example, heat stroke deaths underestimate total deaths due to heat waves. Accidents and freezing underestimate total number of deaths (and hospital admissions) due to snow storms. We need to improved assessment of population effects of extreme events on morbidity and mortality.

What are the aspects of extreme temperature events that most affect health (e.g. maximum temperature, minimum temperature, duration)?

Joint Effects of Temperature and Air Pollution: Environmental stresses are multidimensional. For example, summer heat waves are also likely to be periods of high photochemical air pollution exposures. Winter cold spells are likely to coincide with

infectious disease (influenza) outbreaks. We need to understand the possibility of synergistic effects of extreme temperature, air pollution, and other environmental stresses.

Adaptation: Individuals and populations adapt to changing environmental conditions. High (or low) temperature events that cause increased mortality and morbidity in one climatic area would cause no detectable effect in areas where such events are more frequent. An extreme temperature (or weather) event may produce significantly more mortality and morbidity early in the season, but little effect later in the same season. Need understanding of how average conditions and variance (i.e. frequency of extremes) influence response. What are the time scales for adaptation to occur?

Data and Modeling Issues

Data requirements for assessing health effects of temperature and temperature/air pollution interactions:

- Consistent data on temperature, air pollution and mortality/morbidity in major population centers. These data are available for U.S. and Japanese cities for extended periods. Need consistent data for developing world.
- Surveillance data for possible causes of death which may confound or modify associations, specifically influenza epidemics.
- Assessment of individual heat load exposures and how personal exposures relate to ambient measurements.
- Data on hospitalizations, emergency department visits, outpatient visits, and other health care use, particularly among susceptible subpopulations.

Data required for assessing susceptible populations and adaptation to changes in temperature:

- Data on housing characteristics (e.g. air conditioning) and how these housing characteristics have changed over time.
- Data on social support systems (e.g., percent of elderly living alone).
- Data on behavioral patterns (e.g., percent of time spent exercising outdoors)

Modeling issues:

- Assess characteristics of temperature events responsible for observed health effects (e.g. maximum temperature, minimum temperature, change in temperature, duration of episode).
- Assess adaptation to repeated heat episodes within a season.
- Assess acclimatization to elevated mean temperatures and frequency of heat events over multiple seasons. Assess effects of changes in structural (housing) and behavioral responses.
- Assess how temperature and temperature-air pollution interactions affect life-expectancy.

Programmatic Considerations

- The focus of assessment and research has been in developed countries, e.g., United States and Japan. Most of the burden, however, will fall on populations in developing

countries. We need to expand research and assessment to include developing countries.

- More collective attention needs to be directed by the relevant agencies specifically at the health problems associated with the heat and air pollution effects of global warming.

Recommendations for Japan-U.S.-Collaboration

- Workshop to review state of knowledge of health effects of elevated temperatures and air pollution/temperature interactions and identify gaps in knowledge.
    - Contacts: George Thurston, Larry Kalkstein, Michinori Kabuto
    - Estimated cost: $50,000-$100,000

- Daily temperature, air pollution and mortality data are available for all major cities in the US and Japan going back to the mid-1970's. Comprehensive analysis of temperature effects on mortality in all those major cities using consistent methods. Estimates combined effects over classes of cities and differences in response by housing, climatic, and population characteristics.
    - Contacts: Jonathan Samet, Yasushi Honda, George Thurston
    - Estimated cost: U.S. $1/2 to 1 million per year; Japan $1/4 to $1/2 Million per year; for 3 to 5 yrs.

- Interagency initiative to fund analytic epidemiologic studies of health effects of temperature and temperature/air pollution interactions, taking advantage of naturally occurring events.
    - Contacts: Yasushi Honda, Hiroshi Nitta (NIES), Douglas Dockery
    - US Agencies: NOAA, EPA, and NIEHS; Japanese Agencies: JEA and STA)
    - Estimated cost: U.S. $250K-$500K/year per study; Japan: $250K-$500K/year per study; 3 to 5 years.

Working Group 3: Mechanistic Evidence of Cardiovascular and Respiratory Diseases and Heat Stroke.

Co-chairs: Mark Utell and Mitsuru Ando
Participants: T Creech, D Dockery, M Gant, I Gilmour, H Harasawa, S Hirano, Y Matsumoto, I Uchiyama, J Ultmann.

Scientific issues
This working group identified the following as being key scientific issues:

1. What are the molecular, cellular and physiological responses to meteorological conditions especially higher temperature and humidity, alone, and in combination with air pollutant exposure in healthy individuals?

2. Which of these responses are exaggerated in susceptible individuals? e.g, infant and aged persons and individuals with diseases, especially cardio-pulmonary disease.

3. How do high temperature and humidity exposure conditions (peak versus duration) influence the type and magnitude of response? What are the mechanisms of adaptation/acclimatization to high temperature and humidity?

Data and Modeling Issues
1. Temperature and relative humidity data are available from GHCN in the U.S. National Climate Data Center and AMEDAS (Japan Meteorological Agency).

2. Limited forecasting data are available from the Intergovernmental Panel on Climate Change (IPCC, 2001).

3. At present the models give relatively poor estimates of extreme events and have limited spatial resolution.

4. We identified a need to investigate the effect of temperature and humidity on healthy and susceptible human volunteers and to explore the mechanisms of responses in relevant animal models.

Programmatic Considerations
1. The IPCC has broad responsibility for reviewing scientific evidence on global climate change.

2. There is no coordinating agency responsible for funding joint health research between the U.S and Japan.

3. There is potential for leveraging research coordination and funding with already existing programs on health and air pollution.

Recommendations for Japan-U.S collaboration

1. Perform a comprehensive review and written report of the health effects of meteorological stress especially heat stress, and the potential interactions with air pollutants.
   Contacts: Utell, Ando

2. Convene a joint U.S.–Japan workshop to discuss the findings of the review paper, and generate a focussed research needs document and implementation plan.
   Contacts: Utell, Ando

3. Methods of implementation should include inter-agency funding from the U.S. (DOD, EPA, NIH, NOAA) and Japan (JEA, STA).
   Contact: Piver, Ando

Specific research needs that were identified include:

1. Develop studies to investigate effects of meteorological conditions especially heat stress (together with air pollutants) in animal, human and *in vitro* models. This would include both normal physiology and susceptibility factors including age, gender, genetic differences, presence of diseases especially cardio-pulmonary disease and individual variation in responsiveness.

2. Understand exposure conditions of heat, wind speed, and relative humidity (e.g. peak versus duration) which are responsible for different health effects.

3. Understand the mechanisms of adaptation to meteorological stress
   a. How does one acclimatize?
   b. What factors influence this process? e.g. age, gender, exposure history, health exercise, and socio-economic status.

Working Group 4: Models for Disease, Use in Risk Assessment, How to Incorporate Diversity in Human Population

Co-Chairs: Akihiko Sasaki, Beverly Rockhill
Participants: F. Speizer, W. Piver, J. Longstreth, J. Ultman, J. Last, N. Maynard, C. Portier, M. Fraser, M. Kabuto, Y. Honda

Introduction

Our subjects are to evaluate scientific and programmatic possibilities of modeling health effects and disease worsening related to global environment change. By using such models for risk assessment, description of the structure of adaptation at the population level can be expected beyond the biological and mechanical changes of media and parameters in infectious agents/vectors and in routes of nutritional and hygienic factors. An important question was how to incorporate knowledge of diversity in human populations into such modeling endeavors. "Modeling" was defined to mean quantitative projection of future health patterns based on anticipated social and environmental changes at macro- and micro-scales. It will exceed the technology of conventional exploration or explanation by the logic of present epidemiological studies when faced with the re-analysis or meta-analysis of potentially "terrible" patterns of existing disease data. The complexity is the key to health- and social-related ramifications of available/conceivable parameters and processes. Quantitative uncertainty time and space should be predicted to decide the ability and usefulness of the health effects and disease models. Thus, international collaboration is urgently needed to clarify the similarity and difference in the health and social systems with respect to the total outcome of the living environment and human behavior as well as the ability and efficiency of policy and information in the developing countries .

Scientific Issues

1. Great uncertainties and inconsistencies between these models still exist in the global and regional climate change. As the predisposition of our work, the limitation of statistics and epidemiology, experiments in the present disease modelling practice were were considered. A platform-like model was suggested which enables the combination of the diverse sets of parameters and sectors among various countries as the exchangeable (translatabe) functional units (function tables) and modules (partly autonomic subsystems). And the issue which IPCC TAR could not solve sufficiently were included as the conditions of the model: adaptation, fragility, effects of policy and cost when indoor aritificial environments (e.g., air conditioning) were used extensively.

2. Observational and experimental data on the health effects of many environmental exposures are not operating in a total knowledge vacuum, to project susceptibility and adaptability of individuals or populations to such exposures. Among the many factors affecting them are prevalence of pre-existing disease and known risk factors, socioeconomic factors, access to health care, and to "escapes" from extreme temperatures, solar radiation, and air pollution.

3. To decide the dependent variable of health response, we must consider what are the appropriate outcomes in such models.These are mortality (cause specific or total, incidence of specific diseases, morbidity (whether classified as disease or not), immune system function, daily stress (autonomic nervous condition, especially in urban environment suffered from air pollution). Using the "hard" outcome measure of mortality based on the model without the parameters to assess it, we may capture only the tip of the iceberg of prolonged and propagative health/social outcomes. Global thinking ethically requires information far beyond the original thinking base on the local and cultural limits of available data. To obtain data on a reliable population basis and on scientifically more appropriate measures, we must agree this point before developing both international and global models.

4. Is it possible to anticipate "nonlinear" or "catastrophe" outcomes, such as population disturbances resulting from water or energy scarcities, or outbreaks of infectious diseases caused by changes in local ecologies? We need to go beyond conventional linear regression models of exposure and disease. The need to incorporate complexity into quantitative models of health effects of environmental change is obvious, and the group unanimously agreed that a systems modeling approach, one that allowed for nonlinear, dynamic, feedback-rich relationships between input and outcome variables, is called for. Experimental and observational data on biological mechanisms underlying human responses to UV radiation, extreme temperatures, etc. would be built into such models, but would form only one component of input data. Other components would include factors that influence vulnerability or susceptibility (as listed above); more research is needed here, to better define what these determinants of vulnerability are.

Data and Modeling Issues

1. To incorporate into complex systems modeling, we discussed the need for a foundation to project health effects of environmental change and to model multiple exposures. The goals are to connect the relevant but discrete data in a single systems model (e.g., data on projected trends in air pollution, behaviors such as smoking and outdoor recreation, and use of health care resources), and to anticipate unforeseeable events, especially results of policy response.

2. Other methods discussed were models to incorporate relevant GIS work, statistical/mathematical theory development to handle the uncertainty, and mutidisciplinary development of the software to specify the unit and module approach which enables the shared and even common expressions of the function tables for the actual systems.

3. Procedures for validating/checking models and for examining generalizability of models are needed (e.g., will models built for use in developed countries be appropriate for use in developingcountries?) Likely not--models will likely need to be "local" in terms of projecting health effects (e.g., effects of air pollution and particulate matter are probably different in developed vs. developing countries).

Programmatic Consideration

1. Need to ensure interdisciplinary nature of endeavor beyond public health or epidemiology. For instance, to explain the worldwide increase in asthma incidence and to predict incidence of immune system dysfunctions, we also need expertise of sociologists, demographers, human ecologists, and geographers as well as foregoing specialists. In some cases, perspectives of law and ethics professionals and economists will be needed.

2. International program for developing countries

Recommendations for US/Japan Collaborations

1. Bring together through international workshops modelers from different disciplines.

2. Develop models using existing and developing data from US-Japan data sources to model effects of technology transfer as they interact with environmental change.

3. Develop research and training programs in complex systems modeling.

Report of Session 2 Co-Chairs
Health Effects of Exposure to Ultraviolet Radiation

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Kagoshima University

Four Working Groups dealt with issues surrounding the health effects of increased UVB radiation as a consequence of stratospheric ozone depletion. The participants included representatives from academia, government agencies, and industry with broad expertise in subjects related to UV exposure and its biological and epidemiological consequences. The Working Groups addressed the subjects of UV exposure and action spectra, skin cancer, ocular pathology, and immunological effects as they relate to infectious and autoimmune diseases.

Research recommendations made by each group focused on projects that could be carried out as collaborations between Japanese and American scientists. Feasibility, practicality, and potential benefit to both countries were important considerations in formulating specific recommendations. A recurring theme among the groups was the need to develop molecular and clinical indicators of chronic exposure to UV radiation and to develop models for assessing exposure to UVA and UVB radiation of individuals and populations in different geographic locations. A second common theme was the need to determine the effectiveness of the various wavelengths of UV radiation (action spectra) for each of its biological effects. These two types of information, dose and regimen of UV exposure and wavelength dependence, are essential for assessing the health risks of UV exposure and predicting the impacts of changes in ambient UV radiation. A third theme was the need to conduct more focused workshops with additional experts to refine the specific recommendations and design the optimal experiments to be carried out.

Recommendations from Working Group 5 (UV exposure and action spectra) centered around specific projects designed to improve knowledge about the exposure of individuals and populations to UV radiation and to define an action spectrum for development of cutaneous melanoma. This type of skin cancer represents one of the most serious health consequences of exposure to UV radiation, but the impact of ozone depletion on its incidence and mortality remains unknown because of the absence of information on its relationship to UV exposure.

Working Group 6 focused on epidemiological evidence and mechanisms underlying the role of UVB exposure in skin cancer induction, including melanoma, squamous and basal cell carcinomas, and actinic keratoses (precancerous skin lesions). In addition to collecting data on skin cancer incidence and mortality and UV exposure, this group recommended molecular characterization of skin cancers in American and Japanese populations. They also recommended a study exploring the possible influence of UV exposure on the pathogenesis of infection with human T cell leukemia virus (HTLV) – 1, which is endemic in Japan.

Working Group 7, which dealt with epidemiological and mechanistic evidence associating ocular disease with UV exposure, also recommended collection of better dose-response and wavelength data for various ocular diseases, particularly cataract, pterygium, and age-related macular degeneration. A study of Japanese populations in Japan, Hawaii, and the mainland United States with regard to personal UV exposure and ocular disease was proposed.

The recommendation of Working Group 8, which covered immunological effects of UV radiation, focused on assessing the consequences of UV exposure for the pathogenesis of infectious and autoimmune diseases and assessing the role of UV-induced immune suppression in skin cancer development in Japanese and American populations. Because the best way of assessing the effect of UV exposure on infectious diseases in humans is not readily apparent, a workshop on this subject was proposed as a means of addressing this issue.

In summary, the recommendations of the four Working Groups on health effects of ozone depletion centered around proposals to (1) better define the UV dose-response and wavelength dependencies of these effects; (2) better describe the health consequences of UV exposure; (3) understand the biologic and molecular mechanisms of these effects of UV irradiation; and (4) develop methodologies to assess the health impacts of UV irradiation on populations.

Primary Recommendation for Japan-U.S. Collaboration:
The primary recommendations for Japan-US collaboration are to develop integrated research programs to determine personal UV exposure, prevalence of skin (actinic keratoses and skin cancer) and ocular (cataract and macular degeneration) effects in Japanese populations in Japan, Hawaii, and selected sites in the continental US (Los Angeles, San Francisco and Seattle). The questions to be addressed are:1) the role of UVB exposure in skin and ocular effects; 2) the role of personal behavior in skin and ocular effects; and, 3) the separation of genetic from other factors in incidence of effects.

The benefits of these collaborative studies would be: 1) research results to help shape public health messages; 2) stimulate greater international collaboration on effects of UV radiation exposure; 3) provide a resource for exposure data and modeling studies; and, 4) provide information essential for individual research projects on the health effects of exposures to UV radiation.

Working Group 5: UV Exposure and Action Spectra

Co-Chairs: Masaji Ono, Diane Godar
Participants: J. Herman, L. Wallace, H. Sasaki H. Cyr, T. Creech

Scientific Issues
A number of critical scientific issues were identified in the area of UV monitoring concerning satellite/terrestrial and personal UV dose measurements and correlation of that data with human health risks, such as skin cancers and cataracts, which include:

1) How can satellite data be normalized to existing terrestrial measurements and health effects, such as skin cancer and cataracts, so that satellite measurements may be used to predict health risks in Japan, the US and around the world?
2) How can accurate data be obtained for personal exposure measurements to both UVA and UVB wavelength regions for men and women?
3) Can activity/location written and/or follow-up telephone data survey questionnaires give accurate information of the UV doses people obtain annually?
4) Does the documented data for the incidence of any adverse health effect, such as the potentially fatal melanoma, correlate with personal exposure to UVB and/or UVA?
5) Does the action spectrum for melanoma obtained using a fish model give an accurate prediction for melanoma in humans?

Data and Modeling Issues
1) How accurate are survey questionnaires compared to actual measurements? 2) How can the TOMS satellite data be corrected further to fit the terrestrial data closer? 3) How to choose a representative sample human population in each region of Japan and the US to measure the personal doses of UVB and UVA? 4) Can a suitable (no chemicals), natural (not transgenic) mouse model for the induction of melanoma be developed to replace the existing expensive marsupial model (Monodelphis Domestica)? Does UV correlate with induction of melanoma? If so, how much do UVB and/or UVA contribute?

Recommendations for Japan-U.S. Collaboration

1) Measure personal exposures to UVA and UVB in Japan and the US using the newly developed Japanese device to measure UVA and polysulphone badges or other new devices to measure UVB. A voice-activated recorder with an atomic clock can be included to get activity/location and time-out during the day data. Note that air pollutants can also be measured if other devices are included, e.g., in a shoulder pad. In addition to the voice-activated recorder, a written activity/ location and time in/out data questionnaire and a follow-up telephone survey should be included in this study to know if surveys, or which kind, can be used to accurately predict people's UV exposures. This information is important for predicting the individuals and/or groups of people who may be in a higher risk category for any given UV-related health effect.
    a) People's exposure to UVA and UVB should be measured in the northern, middle and southern regions of Japan and in all four quadrants of the US

b) Both rural and urban areas should be measured
c) All ages 0-100+, four age groups 0-10, 11-21, 22-59 and 60+
d) Men and Women should be measured to compare their different heath risks
e) These personal UVA and UVB doses should be measured for two years using at least two representative weeks during the middle of each season of the year, except during the winter months when UV doses in Japan and the US are minimal
f) Picture or other form of documentation (should also be included in survey questionnaires) of numerous people, especially in cities, during each season of the year to know the extent of UV exposure to different parts of the body. What percent of the Japanese and American populations wear protective clothing, e.g., long sleeved shirts, long pants, hats, sunglasses, umbrellas or use other protection from UV?
Contacts: Ono, Godar, Wallace)
Cost estimate: $3,000,000 for UV measurements in US; $1,000,000.00 in Japan

2) Test and evaluate the already existing personal UVA monitoring devices developed in Japan. Distribute, and/or make these new UVA measuring devices commercially available in the Japan and the US. Compare polysulphone badge measurements to new UVB measuring devices.
Contacts: Ono, Godar, Cyr, Wallace)
Total Cost est. $20,000 for UVA, $20,000 for UVB

3) Terrestrial measurements in Japan and the US can be used to help fine tune the mathematically adjusted TOMS satellite data to obtain accurate doses for UVB and UVA around the world. Using this approach, any UV-related health effect anywhere in the world may be correlated with personal risk from exposure to UVB and/or UVA.
Contacts: Ono, Godar, Herman
Total Cost est. $10,000

4) Correlate the personal UVA and/or UVB doses in Japan and the US with adjusted TOMS satellite data and the incidence of different human health effects, such as cataracts and skin cancers, especially the potentially fatal melanoma.
Contacts: Ono, Sasaki, Ichihashi, Yamaguchi, Godar, Cyr)
Total Cost est. $200,000

5) Use correlated and adjusted TOMS satellite data for the available terrestrial UVA and UVB doses combined with the measured personal UVA and UVB doses in Japan and the US to predict the different UV-related health risks for Asians and Caucasians living in any region of the world.
Contacts: Ono, Godar, Herman, Wallace
Cost estimate: $500,000

6) Obtain action spectrum for the induction of melanoma using a mammalian model, such as the marsupial, Monodelphis Domestica, and/or develop suitable natural mouse model, i.e., not transgenic.
Contacts: Ono, Ichihashi, Godar, Kripke, Ley
Cost est. $1,000,000 to develop a suitable, natural mouse model and obtain an action spectrum for the induction of melanoma.
Cost est. $25,000,000 for action spectrum of melanoma induced in the natural marsupial model, Monodelphis domestica

Working Group 6: Epidemiological Evidence and Mechanistic Evidence of Melanoma and Non-melanoma Skin Cancer

Co-chairs: Masamitsu Ichihashi and Martin Weinstock
Participants: Michinori Kabuto, Suminori Akiba, Yoshihide Kinjo, Chikako Nishigori, Paul Howard, Naohito Yamaguchi, Petra Koken, Margaret Kripke, Margaret Tucker, Frances Noonan, Hidehiko Tamashiro, Masamitsu Ichihashi and Martin Weinstock

Scientific Issues

1. What is the dose-response relation between UV and different types of skin cancer?
2. Why is intermittent exposure important in melanoma and basal cell carcinoma?
3. What are the differences in the relation of UV to cancer by anatomic site of tumor?
4. We need better biologic markers/surrogate endpoints for UV exposure and skin cancer.
5. What is the lag time between UV exposure and the onset of the different types of skin cancer?
6. We need better assessment of individual exposure to UV, and surrogate markers.
7. We need to better define genetic factors and gene-environment interactions, especially but not only for melanoma.
8. We need to investigate clues to mechanisms from study of
    - Immunosuppressed individuals
    - Werner's syndrome
    - Familial melanoma
    - P53 mutations in exposed and non-exposed skin
9. With respect to the patched gene in basal cell carcinoma in Japan, is the association the same as in the United States?
10. What is the reason for the difference in skin cancer risk between Japan and the United States?
    - Skin type
    - Behavior in the sun
    - Genetic factors
11. Why are actinic keratoses increasing in frequency in Japan?
12. How do we improve monitoring of incidence of the keratincyte carcinomas (basal and squamous cell carcinoma) and melanoma in the United States and Japan?
13. What are the mortality trends in the United States and Japan from the keratinocyte carcinomas, and from melanoma?
14. What is the relation between UV and non-skin cancers?
15. What is the UV action spectrum for melanoma and basal cell carcinoma?
16. What is the etiology of acral-lentigenous melanoma in the United States and Japan?
17. How does the proportion of melanoma types vary by latitude in Japan?
18. What are the genetic mutation differences in melanoma in the U.S. vs. Japan

Recommendations for Japan-U.S. Collaboration

I. Descriptive epidemiological study of skin cancer focusing on trends over time in
   A. Mortality, both in the United States and Japan, with joint publication, distinguishing to the extent possible sun related and non-sun related cancers among the basal and squamous cell tumors, and the time trends of acral-lentigenous melanoma or melanoma of the foot mortality in the United States and Japan.
   B. Incidence, both in United States and Japan, of basal and squamous cell carcinoma in selected areas ("sentinel registries"), with investigation of latitude and time trends if possible. Trends in actinic keratosis would also be important to ascertain.

   Contacts: Yamaguchi, Weinstock, Ichihashi, Tamashiro
   Cost estimate: $1 million per year

II. Studies of individual ultraviolet radiation exposure in the United States and Japan to compare objective (e.g. UV badges and film) and subjective (e.g. questionnaire) assessments to include body site-specific information e.g. with use of a mannequin model. A workshop on development of a "minimal questionnaire" instrument i.e. a questionnaire that can reasonably assess UV exposure in a 20 minute interview. Development of an occupational/recreational activity matrix (model instrument) for use as a tool in epidemiologic studies, incorporating geographic, activity, clothing, etc. information for different age groups.

   Contacts: Tucker and Ono
   Cost estimate: $150,000 for workshop, $4 million for study, and $2 million for matrices

III. Molecular epidemiologic study to examine skin cancers in humans in Japan and ethnic Japanese in Hawaii and Los Angeles to look for UV signature mutations in, e.g. p53, patched genes. This could be as a supplement to the LA/Hawaii Multiethnic Cohort study as a nested case-control study within the cohort.
   Contacts: Drs. Henderson, Akiba, Kabuto, Nishigori, Ananthaswamy
   Cost estimate: $4 million

IV. Study of the relation between UV exposure and the prognosis of HTLV-I infection in Japan and the Caribbean islands, with particular reference to viral load, leukemia incidence, and neurologic complications. Discussion also included study of effect of UV exposure on progression of HPV infection to cancer.
   Contacts: Akiba, Kinjo, Hisada (NIH)
   Cost estimate: $3 million

Working Group 7: Epidemiological Evidence and Mechanistic Evidence of Ocular Diseases

Co-chairs: Donald Duncan, Kazuyuki Sasaki
Participants: Hiroshi Sasaki, Janice Longstreth, Sanai Sato, Seymour Zigman, Suminori Akiba, Masaji Ono, Hidehiko Tamashiro, Naohito Yamaguchi, Yoshihide Kinjo

Scientific Issues
There is considerable experimental and epidemiological evidence that UV exposure is important in the development of cataracts, particularly in the formation of cortical cataract. However, a number of key issues remain to be addressed in order to clarify the risk of increased UV exposure due to ozone depletion.

1) A reliable estimation of personal ocular UV exposures must be used. Specific biological markers of exposure to UV-A and UV-B are highly desirable.
2) In contrast to the overwhelming evidence for UV-B, the effects of UV-A have not been well established. Since UV-A exposures of both lens and retina are considerably higher than that of UV-B, more attention should be paid to the effects by UV-A. Further, UV-A may have an additive effect to that by UV-B.
3) Some correlation may exist between the types of cataract and the range of UV spectrum.
4) The importance of UV exposure at childhood still remains unanswered.

Data and Modeling Issues
1) More effort is needed in modeling of personal exposures to UV-A, UV-B, and visible light.
2) A unified cataract classification system should be used, and its validity cross-checked with extant systems. Photographic data should be in electronic form and acquisition geometries must be standardized.

Programmatic Considerations
1) There are a number of concurrent epidemiologic studies in Japan and the US that could benefit from more direct cooperation and interaction among the researchers.

Recommendation for U.S.- Japan Collaboration

1) Population-based epidemiological studies of ocular diseases including cataract, pterygium and age-related macular degeneration should be conducted concurrently in Japan, Hawaii, and the mainland US. The subjects for this study would be 2nd or 3rd generation Japanese over age 50; approximately 2000 participants would be required in each venue. Features of such studies would include the use of personal dosimeters for acute UV-A and UV-B exposures and the use a validated means of determining cumulative exposures. To facilitate collaboration among the various research groups, assessment of cataract should make use of electronic photographic data and subsequent computer analysis in addition to the clinical assessment using the

new WHO classification scheme. Finally, there should be a visual function component of the studies. (Contacts: Sheila West)

2) The relationship between age-related macular degeneration and the role of sunlight is relatively unexplored. This is an important issue that was not addressed adequately in this working group due to lack of expertise among the participants. It is recommended that a workshop addressing this and related issues be conducted. (Contacts: Sasaki)

Working Group 8: Epidemiological Evidence and Mechanistic Evidence of Immune Dysfunction

Co-chairs: Frances Noonan, Chikako Nishigori
Participants: Margaret Tucker, Margaret Kripke, Paul Howard, Martin Weinstock, Janece Longstreth, Masamitsu Ichihashi, Naohito Yamaguchi

Scientific Issues
There is a large body of evidence indicating that irradiation with UV initiates, in experimental animal models, an immunosuppression which plays an important role in skin carcinogenesis and which can modulate the course of infectious diseases. UV has been shown to cause a similar form of immunosuppression in humans, but the challenge is to demonstrate the role of this UV effect in human disease. The major scientific questions which need to be addressed are:

1. The action spectrum for UV immunosuppression in humans is unknown, although action spectra in the mouse are available. Human action spectra information is fundamental for assessing the risks from exposure to sunlight or artificial UV sources
2. There are preliminary indications from experimental studies that there may be wavelength interactions particularly between UVB and UVA modulating UV immunosuppression. Such information is also essential for accurate risk assessment.
3. The major question is the significance in the human population of UV immunosuppression particularly with respect to:
    - Autoimmune diseases
    - Infectious diseases
    - Skin cancer
    - Internal malignancies
    - Vaccination efficacy
4. Genetic Susceptibilities to UV-induced immunosuppression have been described in experimental systems and appear also to exist in humans. The genes controlling susceptibility are as yet unidentified but knowledge of these genes should allow identification of high risk sub-populations
5. The risk factors for UV immunosuppression need to be identified. These may include:
    - Nutritional effects
    - Antioxidant effects
    - Age
    - Skin type
    - Exposure to UV in association with chemical exposure

Recommendations for Japan-U.S. Collaboration

1. Investigate UV immunosuppression of recall antigens in non-melanoma skin cancer, malignant melanoma patients and controls at the same latitude in Japan and the US.
   Contacts: Nsihigori
   Estimated cost: $3 million

2. Investigate the incidence of auto immune diseases as a function of latitude in Japan and the United States
   Contacts: Longstreth, Ichihashi, Horio
   Estimated cost: $150,000

3. To hold a workshop on infectious diseases and UV induced immune suppression including methodologies of determining immune suppressions in humans.
   Contacts: Yamamoto, Longstreth
   Estimated cost: $200,000

Appendices

Appendix A: Program Agenda

8th U.S.-Japan Workshop on Global Change
Health and the Environment: Climate Change and Health Effects of Exposure to Higher Temperatures, Air Pollutant Concentrations, and Ultraviolet Radiation

November 13-15, 2000
Natcher Center, National Institutes of Health
Bethesda, Maryland

Agenda

Monday, November 13

8:00 Co-convenor's breakfast with Session Co-chairs and Working Group Chairs (Room A)

9:00 Continental Breakfast Natcher Center (Room E1/2)

9:30 Welcome and Opening (Room E1/2)

Welcoming Remarks:	Dr. Ruth Kirschstein (Acting Director of the National Institutes of Health)
	Dr. Gen Ohi (Director General of the National Institute for Environmental Studies)
Opening Remarks:	Dr. Warren Piver (Workshop Co-convenor)
	Dr. Michinori Kabuto (Workshop Co-convenor)

10:00 Plenary Session I: Science Overview: Health Effects of Exposure to Higher Temperatures and Air Pollutant Concentrations

Introduction:	Dr. Frank Speizer (Session Co-chair)
	Dr. Yasushi Honda (Session Co-chair)

10:30 Exposure monitoring and modeling
(U.S.: Lance Wallace*, Monitoring personal exposure: a brief review*)
(Japan: Yukio Matsumoto, *Assessing the exposure to air pollutants and higher temperature in Japan*)

10:50 Discussion

11:00 Epidemiological evidence and methods of analysis
(Japan: Yasushi Honda, *Daily temperature and CVD-mortality in Japan*)
(U.S.: Doug Dockery*, Epidemiologic evidence for temperature and air pollution induced morbidity and mortality*)

11:20 Discussion

11:30 Break

11:45 Mechanistic evidence of cardiovascular and respiratory diseases and heat stroke
(U.S.: Mark Utell*, Cardiopulmonary disease and global climate change: potential mechanisims*)
(Japan: Mitsuru Ando, *Effects of extreme temperature in summer on the incidence of heatstroke and hyperthermic disorders*)

12:05 Discussion

12:15 Models for disease, use in risk assessment, how to incorporate diversity in human populations
(Japan: Sasaki, *Ecological consideration in evaluating health impacts of heat waves*)
(U.S.: Beverly Rockhill, *Models for disease, use in risk assessment, how to incorporate diversity in human populations*)

12:35 Discussion

12:45 Concluding remarks (Session co-chairs)

1:00 Buffet Lunch (Natcher cafeteria)
Keynote address (Dr. James Baker, Administrator of the National Oceanic and Atmospheric Administration and Under Secretary for Oceans and Atmosphere)

2:30 Plenary Session II: Science Overview: Health Effects of Exposure to Ultraviolet Radiation

Introduction: Dr. Margaret Kripke (Session Co-chair)

Dr. Sumihiro Akiba (Session Co-chair)

3:00 UV exposure and action spectra
(U.S.: Jay Herman, *UV exposure estimated from TOMS satellite observations*)
(Japan: Masaji Ono, *Personal exposures to UV among Japanese*)

3:30 Discussion

3:40 Epidemiological evidence and mechanistic evidence of melanoma and non-melanoma skin cancer
(Japan: Masamitu Ishihashi, *Epidemiological study on non-melanoma skin cancer of Japanese and Indonesian risk and preventive factors*)
(U.S.: Margaret Tucker, *Ultraviolet radiation exposure as a risk factor for skin cancers*)

4:10 Discussion

4:20 Break

4:35 Epidemiological evidence and mechanistic evidence of ocular diseases
(U.S: Donald Duncan, *Epidemiologic and mechanistic evidence of ocular disease: the Role of Sunlight*)
(Japan: Sasaki and Sasaki, *The significance of an epidemiological study on UV-related human cataract*)

5:05 Discussion

5:15 Epidemiological evidence and mechanistic evidence of immune dysfunction
(Japan: Chikako Nishigori, *Epidemiological evidence and mechanistic evidence of immune dysfunction*)
(U.S.: Frances Noonan, *UV-induced immunosuppression and stratospheric ozone depletion*)

5:45 Discussion

5:55 Concluding remarks (session co-chairs)

6:00 Reception at the Lawton Chiles House
Welcoming remarks: Dr. Sharon Hrynkow, (Deputy Director of the Fogarty International Center)

Dr. Gen Ohi (Director General of the National Institute for Environmental Studies)

Tuesday, November 14

9:00 Continental Breakfast (Center Hall)

9:30 Working Groups 1, 4, 5, and 6 Convene

Working Group 1: Exposure monitoring and modeling for temperature and air pollution induced diseases (Room F1)
Japanese moderator: Yukio Matsumoto
U.S. moderator: Lance Wallace

Working Group 4: Models for disease, use in risk assessment, how to incorporate diversity in human populations (Room A)
U.S. moderator: Beverly Rockhill
Japanese moderator: Sasaki

Working Group 5: UV exposure and action spectra (Room F2)
Japanese moderator: Masaji Ono
U.S. moderator: Dianne Godar

Working Group 6: Epidemiological evidence and mechanistic evidence of melanoma and non-melanoma skin cancer (Room B)
U.S. moderator: Martin Weinstock
Japanese moderator: Masamitu Ishihashi

11:00 Break

11:15 Working Groups 1, 4, 5, and 6 reconvene

1:00 Lunch (Natcher cafeteria, vouchers at registration table)

2:30 Working Groups 2, 3, 7, and 8 Convene

Working Group 2: Epidemiological evidence and methods of analysis for temperature and air pollution induced diseases (Room F2)
U.S. moderator: Doug Dockery
Japanese moderator: Yasushi Honda

Working Group 3: Mechanistic evidence of cardiovascular and respiratory diseases and heat stroke (Room F1)
Japanese moderator: Mitsuru Ando
U.S. moderator: Mark Utell

Working Group 7: Epidemiological evidence and mechanistic evidence of ocular diseases (Room A)

Japanese moderator: Sasaki
U.S. moderator: Donald Duncan

Working Group 8: Epidemiological evidence and mechanistic evidence of immune dysfunction (Room B)

U.S. moderator: Frances Noonan
Japanese moderator: Chikako Nishigori

4:00 Break

4:15 Working Groups 2, 3, 7, and 8 reconvene

6:00 Adjourn

Wednesday, November 15

9:00 Continental Breakfast (Center hall)

9:30 Working Groups reconvene on an as-needed basis (Rooms A, B, G1, G2 to be assigned as needed)

11:00 Break

11:15 Issue Group on Health Effects of Exposure to Higher Temperatures and Air Pollutant Concentrations convenes to hear working group reports, draft report and research recommendations (Working Groups 1-4) (Room E1)

U.S. co-chair: Dr. Speizer
Japanese co-chair: Dr. Sasaki

Issue Group on Health Effects of Exposure to Ultraviolet Radiation convenes to hear working group reports, draft report and research recommendations (Working Groups 5-8) (Room E2)

U.S. co-chair: Dr. Kripke
Japanese co-chair: Dr. Akiba

12:30 Lunch (Natcher cafeteria, vouchers at registration table)

2:00 Plenary Session III: Issue Groups present reports and research recommendations (Room F)

4:00 Adopt report

Appendix B: Abstracts of Science Overviews

Monitoring Personal Exposure: A Brief Review

Lance Wallace
US Environmental Protection Agency

New monitors developed over the past 20 years have made it possible to measure personal exposure to environmental pollutants with improved sensitivity and precision. A new scientific discipline of exposure measurement has resulted. A number of large-scale studies using the new monitors have occurred. Among these are the Harvard 6-City study of respirable particles (PM-3.5), and EPA's TEAM Studies of exposure to VOCs, pesticides, PAHs, phthalate esters, CO, and inhalable particles (PM-10). Recently, studies have begun focusing on subpopulations at greatest risk, such as children (asthma) and the elderly (COPD, cardiovascular problems).

Because people spend most of their time indoors, indoor air quality contributes importantly to personal exposure. Indoor air quality in developed countries has an impact on productivity, with some estimates of up to $50 billion in lost productivity due to poor indoor air quality. In undeveloped or developing countries, however, the main cost is likely to be due to direct health effects. These effects are concentrated among women and children who spend much time near unvented cooking and heating fires using biofuels.

The effect of global climate change on personal exposures will no doubt be complex, and will differ between developed and developing countries due to the different sources of energy employed.

Assessing the Exposure to Air Pollutants and Higher Temperature in Japan

Yukio MATSUMOTO
National Institute for Environmental Studies

1. Monitoring Systems

Monitoring systems are inevitable to assess the population exposure to air pollutants and higher temperature. The constant monitoring of air pollution is indispensable for evaluating the compliance with EQS(environmental quality standards) and for taking the countermeasures against air pollution. In Japan air pollution monitoring was started in 1960's as a basis for air pollution control mainly by the local governments. Meteorological observations, on the other hand, have been conducted since 1860's by the government, initially as part of measures to promote the domestic transport by supplying the meteorological information to escape the natural disasters.

1.1 Air Pollutants Monitoring System

We have two kinds of public monitoring networks viewed in their sponsorship: the one is National Air Monitoring Network sponsored by the Environment Agency and the other ones are Local Air Pollution Monitoring Networks conducted by local governments. The latter monitor the traditional gas pollutants and meteorological parameters, while the former monitors intensively traditional and additional items.

The monitoring stations included in each networks are categorized into general air monitoring stations, automotive exhaust monitoring stations, background air monitoring stations, and source monitoring stations. The general air monitoring stations are to monitor general atmospheric environment, whose location is designed to be about one station per area of 25km^2 in the regions where population density is above a certain value. Automotive exhaust monitoring stations are to monitor roadside environment, and their air sampling inlets are within several meters from the roads. The air which the greater part of people respire in daily life is monitored mainly by general air monitoring stations and partly by automotive exhaust monitoring stations, the data of which are evaluated in comparison to EQS. The number of monitoring stations increased till 1980 and almost saturated near 1980 (for general air monitoring stations, see Table 1).

Table 1 Number of general air monitoring stations and cities (parenthesis) located.

FY	1970	1975	1980	1985	1995	1998
SO2	390(144)	1,359(503)	1,611(617)	1,638(651)	1,620(706)	1,587(703)
NOx	14(9)	666(344)	1,206(546)	1,329(604)	1,462(704)	1,469(717)
Oxidants	2(2)	647(347)	953(485)	1,024(530)	1,134(638)	1,150(648)
SPM*		145(65)	276(131)	784(383)	1,524(703)	1,545(719)
SP**	150(66)	1,037(445)	1,216(527)	67(390)	66(31)	41(16)

* mass density of particulate(< 10 É m). ** density of optically scattering substances.

In Tokyo Metropolitan City, for example, the numbers of general air monitoring stations and automotive exhaust monitoring stations are 27 and 28 in its wards, and 19 and 18 in its suburbs, respectively.

Almost every monitoring site is controlled remotely by local control center by means of telemeter system .The pollutants are measured continuously and automatically giving hourly readings. Part of these data is also opened almost in real time through Environment Agency's and local governments' home pages.

1.2 Meteorological Observation System

Local meteorological observation system has been developed from the viewpoint of preventing the natural disaster by the Meteorological Agency. Meteorological parameters such as temperature, precipitation, hours of sunshine, and wind are observed through several kinds of systems, each covering all over the Japanese Islands. Of the two main systems, one consists of about 150 manned observatories, and the other is a telemeterized network of about 700 automatic observation robots. Tokyo Metropolitan City, for example, has 5 observation points (one manned and 4 robot) in its wards, 5 robot points in its suburbs, and 5 manned points in its islands.

2.Spatial Variations

2.1 Air Pollutants

a) Daily mean(NO2) and 2 days mean (suspended particulate)

For assessing the population exposure to pollutants, it is inevitable to evaluate the order of variances within which the concentration measured at a monitoring point stands for the concentrations of any other points in the surrounding area. We conducted several field surveys in Tokyo Metropolitan City by ad hoc monitoring networks with dense monitoring points. The longer sizes of the survey areas are about 3 to 5 km and the distances between the nearest points were about 1 km. We measured daily averages or 2 days averages on the networks for successive 6 to 10 days, depending on survey.

Analysis of variances of these NO2 concentrations with two factors, i.e. day effect (D) and point effect (P), shows:

- Variance between days (D) was extremely large, i.e. spatial average over a region varies markedly day by day.
- Variance between sampling points (P) was large in comparison with variances due to PÅ~D, i.e. spatial concentration patterns were rather stable and common to all days.
- The magnitude of variations of residuals by removing day effect was, typically, about 3 to 5 ppb (8 – 15 % in C.V.) in winter and about 3 to 7 ppb (12 - 28% in C.V) in summer in terms of S.D. These values indicate the dispersions of NO2 concentrations in a region whose dimension is several km.

For suspended particulate, the analyses show:

1) Day effect(D: day-to-day variation.) was larger than point effect(P: point-to-point variation) for particulate with diameter < 2É m, while two effects(D and P) were of comparable magnitude for particulate with diameter 2 - 10É m.
2) The magnitude of variations of residuals by removing day effect were almost the same for both particulate with diameter < 2É m and particulate with diameter 2 - 10É m: about 6 mg/m^3 in winter and 3 mg/m^3 in summer.

b) Annual mean

We can estimate the station-to-station variation of annual mean by analyzing the results obtained through currently operating network. The dimension of ward area of Tokyo Metropolitan City is about 30kmÅ~30km and one ward's dimension is on the average 5 - 6km. General air monitoring stations are located in 19 wards, among which more than one monitoring stations are located in 9 wards for NO2 and 8 wards for suspended particulate matter(diameter < 10É m). We can decompose station-to-station variations of annual means into two components, intra-ward and inter-ward.

For NO2, intra-ward variation is about 1.5-3 ppb and inter-ward variation is about 5 –6 ppb. This means the tendency that annual averages of nearer stations are closer than those of remote stations. For suspended particulate matter, on the other hand, intra-ward variation is almost the same as that of inter-ward variation, i.e. about 5 – 6 mg/m^3. This implies the difference of particulate annual means at two points does not depend so much on their distance.

These features are stable from year to year. One has to consider these characters to evaluate the population exposure to air pollutants.

2.2 Temperature

For temperature also ad hoc surveys for estimating spatial and temporal variation were conducted in Tokyo Metropolitan area. Analyses are now progressing.

3. Conclusion

In Japan we may say the fundamental conditions for assessing the population exposure to air pollutants and higher temperature are well prepared for both short-term argument and long-term argument. The future progress on our present issue depends on how we collect the health-effect data and combine them with air pollutant data and temperature data.

Health effect of Global Warming: Epidemiological Evidence & Methods of Analysis

Yasushi Honda
University of Tsukuba

Introduction

In Japan, there have been some studies on the relationship between meteorological factors and mortality. Momiyama [Momiyama, 1977] wrote a book on seasonality and mortality, and Inogawa and coworkers reported some analyses [Inogawa and Taga, 1963, for example] using daily mortality information. However, there were no studies that serve as the basis for estimating the health effect of global warming. Hence we began our studies on daily maximum temperature and mortality rate.

Japanese study on daily temperature and mortality

Our first analysis was Kyushu analysis [Honda et al. 1995]. Kyushu is the southern island with 7 prefectures. In this analysis we found the following: (1) 65+ years old age group showed the V-shaped pattern, i.e., the mortality was the lowest at a certain temperature and it became higher when the temperature became extreme. This v-shaped pattern became less obvious when the age of the groups became younger (Fig.1). (2) Both genders showed similar pattern, but females showed lower mortality rates. (3) Temperature-dependent causes of death were circulatory diseases and respiratory diseases. Mortality rate from Neoplasm was constant across temperature categories.

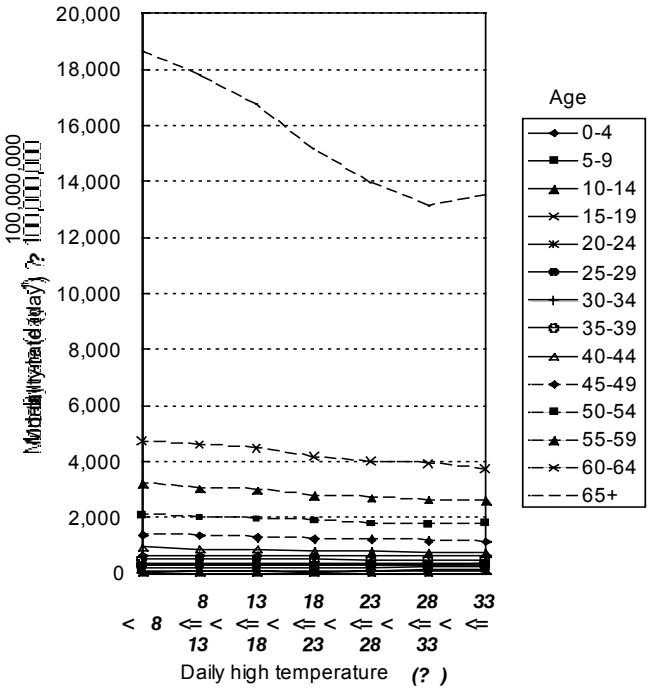

Fig.1 Mortality rate from all causes by daily high temperature and by age
(Kyushu, males, 1972-1990)

In the prefecture-specific analysis [Honda et al., 1998], the V-shaped curve shifted almost horizontally to the right when the climate became warmer. Through this pattern, warmer areas showed lower mortality rate on hot days than colder areas.

Despite the fact that the Japanese population has been aging, the chronological trend of the V-shaped curve was downward in all areas [Honda et al. 1999].

Air pollution study

In our analysis in Tokyo, the V-shaped temperature-mortality pattern moved upward when the daily average carbon monoxide concentration became higher, although the carbon monoxide level was below the regulated value [Honda et al., 1996]. The correlation coefficients of carbon monoxide level and that of other pollutants were less than 0.7, and we considered that carbon monoxide was partially attributable to the elevation of mortality rate.

Harvesting

It is believed that those who die on very hot days are "vulnerable group" that consists of critically ill subjects. In Tokyo, the number of deaths occurred on the days with the daily maximum temperature being 33+ degree C had the linear relationship with the

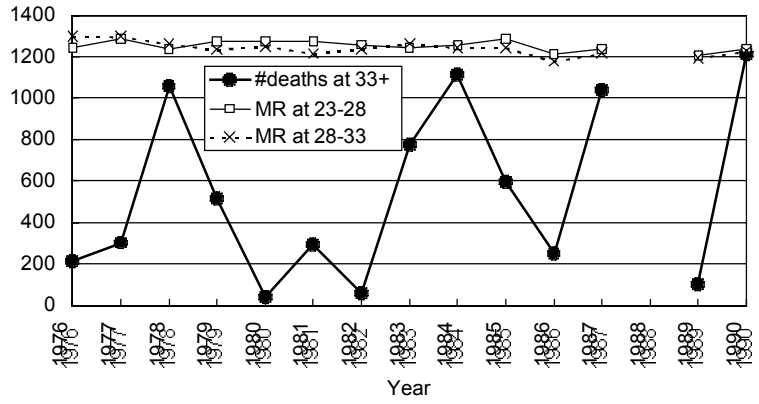

Fig. 2 Number of deaths at 33+ degrees C and Mortality rates at 23-28 degrees C and 28-33 degrees C

number of person-days on the same days. This implies that there was constant supply to the vulnerable group. In addition, as Fig. 2 shows, temperature-specific mortality rates were fairly constant across the years, whereas the number of deaths on very hot days (33+ degrees C) varied substantially. These suggested that harvesting was unlikely.

Future directions

In the above analysis, we did not take account of lag-period (between exposure of certain extreme temperature and death), because our concern was the effect of global warming, and there believed to be small lag-period for heat-related deaths. The lag-period during winter, however, would be as long as a week, because some of the deaths would be related to infectious diseases such as influenza or pneumonia. For evaluating simultaneously harsh summer and favorable winter, we need lag-period analysis.

The drawback of this type of semi-ecological analysis is ecological fallacy. Not only for the validity problems, but also for finding mitigating measures for hotter summer, we need individual level studies.

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Epidemiologic Evidence for Temperature and Air Pollution Induced Morbidity and Mortality

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Atmospheric concentrations of greenhouse gases are rising due to human activities, primarily fossil-fuel combustion. There is concern that the resultant long-term increase in temperature and other climatic changes may lead to direct and indirect health effects (Patz et al, 2000).

Episodes of high temperature produce increased mortality and morbidity, particularly among the elderly. Behavioral adaptation can reduce morbidity and mortality due to heat. Adaptation is seen in temporal analyses by reduced effects as the summer season progresses, and in spatial analyses by reduced response in regions with a higher frequency of heat episodes. Cold temperatures also are associated with increased morbidity and mortality, primarily through effects of longer-term average cold temperatures rather than episodes. It is expected that milder winters would significantly reduce total numbers of deaths annually.
Increased temperatures may indirectly affect morbidity and mortality through changes in air pollution concentrations. In the United States, the most serious air pollution problems now are associated with summer-time photochemical oxidants. High temperatures promote the photochemical production of ozone. These same photochemical reactions also produce sulfate and nitrate fine particles. Increased use of air conditioning to adapt to higher summer temperatures will increase power plant emissions of ozone and fine particle precursors. Increased acute morbidity and mortality has been associated independently with both ozone and fine particle episodes.

The fossil-fuel combustion processes that produce CO and other greenhouse gases also produce air pollutants such as particulate matter, sulfur oxides, and nitrogen oxides. Recent epidemiologic studies have shown that these air pollutants are associated with increased mortality and morbidity, even at the modest levels seen in developed countries today. Reduction of fossil fuel combustion to reduce greenhouse gas emissions would be expected to produce substantial immediate improvements in air quality. The Working Group on Public Health and Fossil Fuel Combustion (1997) predicted that 700,000 fewer deaths world-wide would occur annually from reduced particle air pollution exposures alone under “business as usual” forecasts compared to strategies to limit green gas emissions.

Thus there are significant and substantial direct effects of air pollution that would be avoided with reduced fossil fuel combustion.

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Cardiopulmonary Disease and Global Climate Change: Potential Mechanisms

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Climate change is one of a multitude of factors that are likely to have significant influence on human health over the next century. Increased temperature as well as increases in criteria pollutants or potentially new pollutants may aggravate disease. Despite the expanding evidence for global warming, the biologic mechanisms by which interactions of air pollution and increased temperature affect the cardiopulmonary system are uncertain. Plausible hypotheses include increased airway inflammation, induction of acute phase responses, induction of heat-shock proteins, alterations of neurogenic responses, and altered host defense mechanisms.

Pollutions at risk: Several lines of evidence suggest that persons at risk from health consequences of global warming are those with severe heart and lung disease and perhaps the elderly. Persons with coronary artery disease have atherosclerotic narrowing of the coronary arteries, which deliver blood to the heart. Cardiovascular disease accounts for nearly 45% of U.S. mortality and much more morbidity; it is frequently complicated by congestive heart failure. Although the incidence and severity of coronary heart diseases increases with age, it is not a disease limited to the elderly.

Persons with chronic obstructive disease (COPD) have physiologically significant impairment of lung function, most often from underlying emphysema and airway narrowing caused by smoking. The term COPD encompasses various pathophysiological states (emphysema and chronic bronchitis) associated with obstruction to air flow. The obstruction is relatively fixed, differentiating this condition from asthma, in which reversibility or variability in air flow obstruction is a cardinal feature. In the U.S., COPD accounts for 13% of hospitalizations and is the fifth leading cause of death and climbing.

In contrast with COPD, asthma is often a disease of the young and otherwise healthy; the incidence is highest in the first 10 years of life. It is a very common condition, affecting up to 10% of the U.S. population. Moreover, not only are the incidence and prevalence increasing, but based on the increase in asthma hospitalizations, the severity and acuity of the disease seems to have increased. The hallmark features of asthma are reversible airway obstruction, hyperresponsiveness and inflammation. A growing body of evidence implicates an allergic sensitization in the etiology of asthma.

Potential Mechanisms of Cardiopulmonary Responses: There is no established mechanism to explain the relationship between pollutant exposure and excess cardiovascular mortality. Recent studies in healthy and compromised animals and preliminary data in humans have suggested that inhalation of particulate matter may induce changes in cardiac rhythm or repolarization. It is conceivable that increased temperature could produce similar effects or exacerbate the responses to pollutants. Furthermore, studies in humans and animals indicate that increased temperature may induce vasodilatation leading to increased cardiac demands; this could translate into clinical congestive heart failure in individuals with underlying coronary artery disease. Increased temperature may also induce heat-shock proteins which could either be cardio-protective or contribute to a systemic inflammatory response. Although there is little to suggest that exposure to air pollution has direct cardiac effects, increased temperature may increase ozone levels through atmospheric photochemical reactions. Increased ozone exposure results in altered airway permeability and increased penetration of small particles or the reaction products into the systemic circulation, with induction of inflammatory cytokine expression in the myocardium. This could contribute to myocarditis or epicarditis, or progression of coronary artery disease. Furthermore, an acute inflammatory response in the airway may be accompanied by an acute phase response, with increases in plasma viscosity and blood coagulation factors, such as fibrinogen, Factor VII, and plasminogen activator inhibitor. Such events could result in increases in heart rate, changes in heart rate variability, contribute to congestive heart failure and arrhythmias, or participate coronary events in the individuals with coronary artery disease.

Similarly, the mechanisms by which global climate change could adversely affect patients with asthma and COPD have not been determined. Individuals with asthma and COPD have disease characterized by

increased airways resistance. Increased temperature could increase the work of breathing; this could result in increased ventilation, atelectasis, hypoxemia and disease exacerbation. Furthermore, as previously noted, increased temperature might be associated with increased levels of ozone and particulate matter pollutants. Pollutant exposure could contribute to progression of disease by enhancing airway inflammation. It is conceivable that new fuels and new technologies would lead to increased levels of airborne metals. A mechanistic model for particle-induced lung inflammation involves injury to the epithelial cells by reactive oxygen species, enhanced in the presence of metals via Haber-Weiss and Fenton chemistry, accompanied by activation of nuclear regulatory factors, leading to elaboration of pro-inflammatory cytokines, including IL-8 and IL-6. This in principle could also result in activation of vascular endothelium and circulating leukocytes. Alternatively, increased temperature could enhance susceptibility to infectious complications by modifying normal host defenses, e.g., impaired mucociliary clearance, increased adhesion of bacteria to epithelial cells, altered alveolar macrophage function, or impairing specific or non-specific functions of the immune system.

The research effort to understand mechanisms of global climate change on cardiopulmonary disease has been limited; it offers unique opportunities for meaningful collaborations between basic scientists, epidemiologists and clinical investigators.

Effect of Extreme Temperature in Summer on the Incidence of Heatstroke and Hyperthermic Disorders.

Mitsuru ANDO

Human activities such as combustion of fossil fuel, deforesting operations and agricultural activities are responsible for the rapid increase of anthropogenic greenhouse gases emissions. For human health, it is evaluated that global climate change may have a critical on the increased of severe heat stress in summer and spread of some infectious diseases. The health effects of heat stress include heatstroke, hyperthermic disorders and dysfunction of the immune systems.

Ecological Consideration in Evaluating Health Impacts of Heat and Temperature

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The purpose of ecological consideration on health impacts by climate change and especially of heat and temperature is to check the similarity and difference in the natural and artificial conditions (e.g., air conditioning) between the U.S. and Japan. Differences in the way of using artificial environment and of modification by culture and regime, either traditional or prevalent, related with heat/temperature adaptation as the society. However, Asian countries will claim against the too simplified discussion based on the crude but efficient social systems. Before set up of disease models of heat suffers, I want to clarify what is common and how we can assess health risks from examples, because it is the international aspect against the global consideration required for climate change impacts.

Methods and Results

I. R-R interval (represent autonomic vervous functions related with body heat balance) of workers during the dry and hot seasons in Bangkok was described as the adaptation to temperature environment in daily indorr and outdoor life.

II. Analysis of ecological background observed in accidental deaths of small children left in parked cars during parents' shopping and pinball games shows another unconceived risk by solar radiation (Rt) and ambient temperature (Ta).

III. A concept of interaction between social system and living environment is described which may effect on the disease model for climate change. Because it may exceed the simple biological mechanisms when we have to develop a primary (zero order) prevention system for adaptation options against climate change in various countries and regions. Table 1 can be extended by several principles and research as follows:

- To describe and relate adaptation capacity and mechanism against disease and stress.
- To evaluate perception and behavior by age, sex and occupation as personal adaptation options.
- Notion of the risk mechanism should be described for social adaptation by declaration, monitoring, emergency service, education/forecast, and technological control.

Conclusions

I. U.S.-Japan cooperation: urban maps against heat exposure and AC availability

II. To describe health adaptation (on human, by human, and for human) as interactions of materials and systems with human subpopulations, which has depth and time-scale of risks.

III. To judge the adaptation, information on criteria, time-scale, and effecting factors are required.

IV. To standardize data and mechanisms to worsen chronic diseases (diabetes, dialysis, advanced cancer, feeding disability, and senile disease), especially its notions and indirect relationships.

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Models for Disease, Use in Risk Assessment, How to Incorporate Diversity in Human Populations

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The focus in much of epidemiology now is on attempting to identify causes of individual cases of disease. This focus on individual risk is gaining strength precisely at a time of growing global environmental threats, ecosystem disruption, and widening social and health inequalities, and it may render the public health community less effective with respect to addressing such challenges. These challenges will require confronting the uncertainties of working with anticipated exposure scenarios rather than with current and readily-measured exposures, and quantifying effects, which may not become evident for decades, of complex, feedback-rich systemic disturbances of natural systems. As McMichael notes[1], most of the potential health impacts of global environmental change will not arise via the familiar locally-acting toxicologic mechanisms that scientists are well prepared to study. Rather, anticipated health impacts would result mainly from perturbations of natural geochemical and ecologic systems. These effects would impinge on whole populations, and many would entail long time horizons. These effects will likely fall, disproportionately, on poorer countries, which are ill-equipped to monitor both environmental changes and resulting changes in disease burden. In short, the emerging concerns over potential health consequences of global change refer to impacts on populations, and not risks for individuals.

In this talk, I will discuss the conceptual and quantitative reasons why epidemiologic risk models are more properly suited to questions regarding causes of incidence of disease in populations, and sources of variability in health outcomes, than to questions regarding specific individual-level etiologic mechanisms and biological pathways. Statistical risk models perform poorly at this latter task, and this will likely continue to be the case despite the “promise” of genetic and molecular data.

Because most chronic disease risk factors, including exposure to air pollutants and excessive heat, have only modest associations with disease incidence and mortality at the population level (i.e., relative risks often between 1.2 and 3.0), they are very poor at discriminating between individuals who will, and who will not, develop disease or die from a particular disease. I will present quantitative illustrations of this point. Risk factors identified in statistical models are probabilistic concepts; risk factor findings are thus by necessity couched in probabilistic language. "Cause" and "prevention," as they pertain to risk factor logic, are concepts that apply to aggregates of individuals, and risk modeling should thus point the way to macro-level interventions to shift distributions of risk factors within populations or population subgroups.

A separate issue related to modeling that is of concern to this group is that of criteria used to identify a good model. The assumptions underlying risk models are usually addressed in one of three ways[2]: with formal statistical hypothesis testing or confidence interval estimation; with more informal comparisons against existing observational or experimental evidence; and with simple faith, as occurs when evaluation of assumptions would require data that are not, and may never be, available. Errors associated with the first two kinds of assumptions can often be reasonably quantified. Error due to the third kind of assumption is by definition not assessable, and often one is unable to determine even whether this error is a trivial component of the overall model error or its most important part. Further, and obviously, this difficulty grows with the model’s complexity: for a given amount of data, the extent to which assumptions can be verified decreases as the number of assumptions increase[2]. Because estimating the human health effects of global environmental change will entail working with a variety of potential scenarios, rather than with existing data, model assumptions will often not be verifiable. In this setting, epidemiologists and other medical scientists might benefit from the methodological contributions of demographers, who over the past decades have improved mathematical and statistical methods for projections and forecasts, and who are accustomed to giving a range of projections, pertaining to high, medium, and low exposure scenarios. Demographers have also developed sophisticated techniques of indirect estimation. These techniques are applied in situations when data are incomplete and/or scanty, as would likely be the case in developing countries with regard to data on both environmental change and human health responses.

These modeling issues, of discernment of individual-level etiologic mechanisms versus prediction of incidence and description of variability, and of developing criteria for identifying good models, will form the basis of this talk.

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UV Exposure Estimated from TOMS Satellite Observations

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NASA

The global coverage afforded by satellite estimates of UV irradiance can be used to distinguish regional and global changes in contrast to purely local observations from ground-based instruments. Daily global maps of UV-erythemal irradiance (290 to 400 nm) at the Earth's surface can be obtained using the ozone amount, cloud transmittance, aerosol amounts, and surface reflectivity from the solar UV radiation backscattered from the Earth's atmosphere as measured by TOMS (Total Ozone Mapping Spectrometer) and the independently measured values of the extraterrestrial solar radiance. The variability in daily irradiance values at a given location is caused first, by partially reflecting cloud cover, second, by haze and absorbing aerosols (dust and smoke), and third, by ozone. There are major reductions of UV irradiance caused by the presence of aerosols. These reductions can exceed 50 ±12% underneath the absorbing aerosol plumes in Africa and South America (desert dust and smoke from biomass burning), and exceeded 70 ±12% during the Indonesian fires in September 1997 and again during March 1998. Recent biomass burning in Mexico and Guatemala have caused large smoke plumes extending into Canada with UV reductions of 50% in Mexico and 20% in Florida, Louisiana, and Texas.

Maximum UV exposures occur at high altitudes. While terrain height is a major factor in increasing the amount of UV exposure compared to sea-level, regions such as Australia, that have large numbers of cloud free days have UV exposures rivaling those at cloudier higher altitudes. Extended land areas with the largest erythemal exposure are in Australia and South Africa where the number of clear-sky days can be more than 300 per year. This is in contrast to similar latitudes on the East Coast of the US where cloudy days are more frequent. The regions of high UV exposure are known to cause an increased incidence of skin cancer and cataracts. Australia is a prime example of the human health problem that can result from excess exposure for a UV sensitive population. To a somewhat lesser degree, the same problem exists in the US, especially in the southwest.

The large short-term variations in ozone amount that occur at high latitudes can cause changes in UV irradiance comparable to clouds and aerosols for wavelengths between 280 nm to 300 nm that are strongly absorbed by ozone. These changes affect the health of human populations in Canada, Scandinavia, and parts of Russia. There are also effects on the yields of agricultural products and ocean life.

The geographic distribution of monthly-averaged UV irradiance from 290 to 400 nm weighted by the CIE erythemal action spectra can be illustrated by maps for the following months, a: January, b: March; c: July, and d:September.

Current Situation of Ultraviolet Radiation in Japan: Monitoring, Exposure and Prediction

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Abstract: Although we have many data and the knowledge of ultraviolet (UV) radiation at ground level, we only have limited data and knowledge of UV exposure. It is well known that there are big discrepancy between UV radiation at ground level and residential UV exposure. Here, I briefly summarize the current situation and future prediction of UV radiation in Japan and present some findings relative to UV exposure.

1. UV monitoring in Japan

JMA=s UV monitoring

In Japan since 1 January 1990 Japan Meteorological Agency (JMA) has been monitoring UV-B irradiance at ground level at four monitoring stations (Sapporo: 43–North Latitude, Tsukuba: 36–N, Kagoshima: 32–N, and Naha: 26–N) using a Brewer spectrophotometer. Regarding the geographical distribution of UV-B irradiance in Japan, we can find distinct gradation corresponding to latitude. UV-B irradiance at ground level clearly shows a seasonal (strong in summer and weak in winter) and a diurnal (higher intensity in the noon time) fluctuation. From these results, we can infer that 70-80% of yearly UV-B irradiance is observed within the summer season, April to September, and 60% (summer) to 70-80 % (winter) of daily UV-B irradiance during midday, _2hours around the local noon.

NIES UV monitoring network

From 1 January 2000 a new UV monitoring network has started with the cooperation of about 20 organizations, i.e., NIES and other national and/or prefectural Institutions and Universities, from all around Japan. Broad band UV radiometer (MS-210W, MS-210A, EKO Ltd.) were used and the network members were selected from the viewpoint of geographical distribution and some other aspect such as UV-related epidemiologic studies.

2. Measurement of UV exposure

We carried out a longitudinal UV exposure measurement. Field surveys were conducted in 4 areas, and 20 outdoor workers (caddies at golf links) in each area were selected as participants. UV exposure measurements were carried out throughout the year and daily accumulative amounts of UV exposure were measured using simple device (Model SUB-T, Toray Techno Inst.) which can measure UV radiation of 260-390 nm wavelength, being attached to clothes near the chest.

The levels of UV exposure obtained through field survey showed good agreement to those of UV radiation on the whole but they showed great difference among subjects.

3. Estimation of UV exposure

UV exposure mainly depends on the UV irradiance at ground level and the time spent outdoors. Behavioral characteristics of subjects, such as clothing and whether or not a hat and glasses are worn also play important roles. Here, I will discuss some of those factors.

3.1 Efficacy of the short questionnaire to estimate outdoor activity

To determine the outdoor activity pattern of subjects throughout their whole lifetime is very important for estimating UV exposure, but is very difficult. I tried to simplify the outdoor activity record. One-week surveys, in which schoolchildren were asked to record their daily outdoor activity patterns every 15 minutes, were carried out. Using these data I discussed the effectiveness of a short questionnaire in evaluating the outdoor activity for estimating UV exposure instead of detailed information on actual outdoor activity patterns.

The estimate of the number of hours spent outdoors in a whole day will give a good correlation to, but smaller estimates than, that obtained using the original outdoor activity pattern. I found that the number of hours spent outdoors between 9:00 and 15:00 gives the best estimates, not only a good correlation to but also values of the same order as those obtained using the original outdoor activity pattern.

3.2 Reevaluation of protective measures (Mannequin Study)
Although wearing glasses is recommended as a preventive measure against UV-related eye diseases, there has not yet been sufficient evidence on its efficacy. To evaluate the effectiveness of protective measures, such as wearing a hat and/or glasses, against UV exposure of the eye, we developed a new experimental system.

Two mannequins, with and without protective measures, are controlled by computer and move synchronously following the scenario of actual movement of a human head which was input to the computer in advance. In the experiment, we continuously measured UV exposure levels using small UV sensors attached at different points on the mannequins. Compared to the ocular UV exposure level without glasses or a hat, the ocular UV exposure level with glasses and with a hat were averages of 8.8% and 80.8% over 30 minutes, respectively. This means that the use of glasses and hats could reduce the UV exposure of the eye 90% and 20%, respectively.

3.3 Estimation of ocular UV exposure for the participants of epidemiologic survey
For the participants of epidemiologic survey, which was carried out in an area (Kikai Island, Kagoshima) with the cooperation of Kanazawa Medical University, UV exposure was assessed using the above-described results. Although all participants have nearly the same residential history, estimated cumulative UV exposure was widely distributed, and about 40% of the subjects were classified into the lowest range. These suggest that the large difference in estimated UV exposure levels is mainly a result of differences in their outdoor activity patterns. Differences in UV exposure levels were observed for age (higher in elder people) and jobs (higher in farmers, people in transportation and sales) but not for gender.

Key Words: ultraviolet(UV), monitoring, exposure assessment, outdoor activity, lifestyle

Epidemiological Study on Non-melanoma Skin Cancer of Japanese and Indonesians Risk and Preventive Factors

Masamitsu ICHIHASHI, Keishi ARAKI, Masato UEDA, Naohito YAMAGUCHI and Suminori AKIBA

1. Introduction

Chronic sun exposure is responsible for skin cancer induction and premature aging of the skin. Skin cancers are epidemiologically shown to be the most common cancer not only among light-skin populations, but also in male of Indonesian with pigmented skin. Basal and squamous cell carcinomas (BCC and SCC) are the most common among skin cancers, and BCC on sun-exposed area occupies nearly 80% and 65%, of the total skin cancers among Caucasians and Asians, respectively.

Epidermal cells exposed to solar UVR exhibit a number of DNA damage, primarily in the form of covalent linkage between adjacent pyrimidines, as cyclobutane pyrimidine dimers and (6-4) photo-products caused by direct absorption of UV light, and purine photooxidation caused indirectly by reactive oxygen species. These damages primary are responsible for the induction of base changes in its daughter strand at the opposite site of pyrimidine dimers, leading to gene mutation and carcinogenesis.

In this workshop, the prevalence and incidence of pre-cancerous lesions and cancer on sun-exposed skin of Japanese is discussed based on epidemiological study in two locations in Japan.

Risk and preventive factors suggested from case - control study on skin cancer in Indonesia and Japan will be also discussed.

2. Epidemiological Study on Skin Cancer

A large body of circumstantial evidence has been accumulated supporting a role of sunlight to induce skin cancer in humans: (1) more frequent in residents of areas of high ambient solar irradiance, (2) more frequent in sun- sensitive people, (3) occur mainly on sun-exposed body site , (4) more frequent in people with high sun exposure, (5) more frequent in people with benign sun-related skin conditions, and (6) reduced by protection of the skin against the sun.

Epidemiological studies on skin cancer were primarily conducted to elucidate the incidence rate of light-skinned Caucasians. To our knowledge, there is no detailed report about skin cancer incidence or prevalence rate on sun-exposed area in Asian including Japanese, except disease rate, or incidence rate calculated from mortality rate or incomplete registration.

An examination of the occurrence of skin cancers and pre-cancerous lesions among residents of Kasai City (34” degrees 56' N) since 1992 through 1999, and of Ie-island (25 degrees 10' N) since 1993 through 1999, has been conducted to characterize the prevalence and incidence of skin cancers in Japanese people and to evaluate risk and preventive factors. Participants in municipal regional health examination were seen by dermatologists. Final diagnosis was made histopathologically. Participants were also interviewed by means of a questionnaire.

The mean prevalence of actinic keratosis (AK) in residents of Kasai City and Ie-island was 166.7 and 756.26, respectively, indicating that twice the annual dose of UVB radiation in Ie-island causes a 3~4 fold higher incidence of AK, although life styles, including types of occupations, differ in these two locations.

The incidence of AK of subjects working outdoors, having Japanese skin type I, having a history of severe sunburns during childhood or having 6 or more seborrheic keratosis on sun-exposed areas was statistically higher than that of subjects working indoors, having Japanese skin type III, having no history of severe sunburns, or having less than 5 seborrheic keratosis, respectively. AK incidence of the female who used cosmetics every day after 20 years of age was significantly lower than that of the subjects who did not use. The prevalence of AK per 100,000 Japanese in Kasai City has decreased every year, from 414.3 in 1992 to

86.8 in 1995. The incidence of AK in Kasai City also decreased from 1990 to 1997, suggesting that our educational campaign for residents informing them of the adverse effects of sunlight and the efficacy of sunscreens in protection against skin cancers, has contributed to the reduction of AK in Kasai City.

7 and 13 cases of skin cancers were found in residents of Kasai City (from 1992 to 1999) and on Ie-island (from 1993 to 1999), respectively. These numbers indicate that people living in areas of higher ambient solar radiation have a higher incidence of skin cancer, but are too small to be used to calculate a reliable prevalence of skin cancer in Japanese, but suggest that the prevalence rates of NMSC of Kansai city and Ie-island per 100,000 population are around 20 and 90, respectively.

Our epidemiological study indicates that Japanese skin type 1, subjects having seborrheic keratosis over 6, or having experience of severe sunburns during childhood may be risk factors for pre-cancers, and possibly for non-melanoma skin cancer of Japanese.

3. Case control study on skin cancer of Indonesian and Japanese.
To further study risk and preventive factors of skin cancer of Japanese and Asians, we started the Indonesia-Japan epidemiological Joint study on skin cancer, focussing on case-control analysis since 1995. We have collected approximately 150 cases and 250 controls of Indonesian subjects in Jakarta. Low education and outdoor workers are found to be risk factors, and garlic, fresh fruits and vegetables were suggested to be protective factors for NMSC of Indonesians. Skin cancer cases and controls of Japanese are still too small for statistical analysis of risk and preventive factors of Japanese, although multi-center study on case- control of skin cancer has been going on since 1998.

4. Future problems to be solved
The epidermiological study on skin cancer of Japanese and Asians has not been fully conducted, except our skin examination study in two locations (Kansai city and Ie-island), and case-control study in Jakarta. The data of skin cancer incidence of Japanese published by IARC is not reliable, since registration system has been almost incomplete.

To clarify the risk and preventive factors of skin cancer for Japanese and to contribute to keeping healthy and young skin of Japanese, a large scale case-control study supported by the Government should be conducted in the near future.

Ultraviolet Radiation Exposure as a Risk Factor for Skin Cancers

Margaret A. Tucker

Skin cancers result from the complex interaction of environmental exposures and host susceptibility factors. Rates of melanoma are highest in whites in high sun areas, but also differ in Japanese in different geographic locales. Although sun exposure is the primary environmental exposure related to both melanoma and non-melanoma skin cancers, individual ultraviolet exposure measurements remain problematic. Many non-melanoma skin cancers occur in areas of skin heavily sun-exposed, but melanomas do not. Although early childhood sun exposure as the dominant risk factor for melanoma has almost become dogma, there is a growing body of evidence that adult exposure also plays an important role in melanoma development. The risk of melanoma varies widely by host factors as well. Several genes predisposing to melanoma have been identified. Those with high risks in whites include *CDKN2A*, *CDK4*, and *RB,* all of which are autosomal dominant. Among Japanese, the most common genetic variations leading to increased melanoma risk are the autosomal recessive conditions of xeroderma pigmentosum and Werner's syndrome.

The Significance of an Epidemiological Study on UV Related Human Cataract

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Although the scenario of cataract induced by solar Ultra Violet rays (UV) is still being discussed in the lens research field, based on my own data, current topics on human cataract in Japan will be briefly discussed from the standpoint that the scenario has been accepted.

1. The current state of cataract patients in Japan

With the great increase in the aged population and the rapid progress of medical treatment, medicare costs have constantly been rising in Japan. According to the reports of periodical governmental investigations (conducted every 3 years), the number of patients with cataract receiving medical treatment has ranked as the top fifth disease (excluding dental disease) for the past few years. Furthermore, the increasing ratios from 1990 to 1993 and 1993 to 1996 were 16.9 % and 18.7 %, respectively, and this ratio may continue for at least 10 more years. Consequently, this fact is directly linked with medical finance, since the present treatment for cataract is limited to surgery.

2. On-going epidemiological cataract surveys

An ecological cataract survey has been in progress as a part of the study
of "Global Environment Research" with the support of the Environment Agency. The study has been performed as an International Cooperative Study during the past five years. The survey places are Noto, in central area of the main Island of Japan, Sapporo in northern Japan, and Amami and Okinawa, in the subtropical area of Japan, as well as Singapore, and Reykjavik (Iceland). All the surveys are population based and the Noto and the two cooperative studies applied a randomized sample collection. From the standpoint of UV irradiation dosage (Erythemal UV: TOMS), that of Reykjavik is around one third that of the Noto area in Japan and 1 / 6 that of Singapore. The cortical cataract prevalence by age in the Japanese subjects of Noto is significantly higher than that of the Icelanders. Even though an association between cortical cataract prevalence and solar UV cannot be simply made due to several differences such as race and life style, this data may be attractive.

3. Individual solar UV exposure as a risk for cataract formation and/or progressionin the general population

Although the above ecological study may support the scenario of solar UV induced human cataract, it is insufficient as epidemiological proof. What is required from a UV related cataract epidemiological study today is proof of individual solar UV exposure in the general population as a risk for cataract formation and/or progression in the general population such as the recent Salisbury Study (West et al.). In Iceland, where the yearly irradiation dose of solar UV is low, we found that solar UV exposure is still a risk for cataract.

4. The significance of applying a unified cataract classification system

Not only in industrialized countries, but also in developing countries, the increased number of cataract patients poses serious problems, since globally, cataract is a top ranked cause of blindness. To establish an adequate strategy, prevalence or incidence studies are essential. In fact, although these surveys have been performed in most industrialized countries, different classification systems have been applied. Consequently, a direct comparison of data between the surveys is often difficult.

With the leadership of WHO, a new cataract classification and grading system was proposed recently this year. (Thylefors, Chylack, Konyama, Sasaki, Sperduto, Taylor and West). Due to this measure, epidemiological studies of cataract from now on should apply this unified classification system.

Epidemiological Evidence and Mechanistic Evidence of Immune Dysfunction

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Cancers are thought to be caused by accumulating several DNA damage in crucial genes such as oncogenes and/or tumor suppressor genes. Solar ultraviolet light induces human skin cancers and action spectrum of UV carcinogenesis falls into UVB. Using *in vitro* assay systems such as plasmid, *E. coli* and shuttle vector, UV, especially UVC, is well known to cause DNA damage like cyclobutane-pyrimidine dimers and (6-4) photoproduct, which are reported to be major classes of DNA lesions involved in the cytotoxicity and mutagenesis inducing preferentially transition type mutation at dipyrimidine. Unrepaired or misrepaired UV-induced DNA damage that leads to mutations and alterations in DNA structure during replication may trigger carcinogenesis if it occurs in specific target genes. The frequency of *p53* mutations of NMSCs from sun-exposed area and non/less sun-exposed area revealed almost comparable. However, 67 % had the transition at dipyrimidine sites in NMSCs from sun-exposed area, whereas only 20 % had the same type of mutations from non/less exposed area (p< o.o5), which strongly suggests UV indeed cause mutations. Recently, carcinogenesis by UVA has been pointed out. In *in vivo*, possibly in the presence of endogenous photosensitizers, DNA damage other than dimers, such as 8-OHdG, formed indirectly via ROS could be involved in UVA induced skin cancer. Epidemiology and mechanisms of human UVA carcinogenesis remains to be clarified.

There are an ample evidence in animal models that exposure to UV impairs the function of immune system. In mid-1970s, Kripke first pointed out the association between the immunosuppressive effects of UV and carcinogenesis. Experimentally, irradiation of mice with UV produce skin cancer. UV induced mice skin tumors are highly antigenic and they are easily rejected when transplanted to normal syngenic immune-competent mice. Then, why those tumors grow progressively in the host (UV irradiated) mice. The explanation for this is that the UV suppresses the immune surveillance system for rejecting "non-self" cancer cells and allows the highly antigenic tumors to grow progressively. It indicates that UV is carcinogenic not only by inducing mutations at the crucial genes, but also by circumventing immune surveillance against skin cancers by modulating the immune response in a way that favors tumor development. Studies of animal models demonstrate that UVB irradiation (500 J/m2 x 4 or 2 kJ/m2), which resemble quantitatively and qualitatively the manner in which human beings experience sun-bathing or sun exposure, produces local, nonspecific immune suppression that inhibits immune effector functions within irradiated skin, and larger dose (5 kJ/m2) impairs systemic, specific immune suppression against antigen introduced at a critical time after exposure to UV radiation. Systemic suppression of immune surveillance could cause internal malignancies as well. Evidence is presented suggesting that production of cytokines by epidermal cells in response to UV induced DNA damage is an important component of UV induced specific immune suppression. Therefore, DNA damage is involved in UV carcinogenesis not only by causing mutation on the crucial genes, but also suppressing immune response. The point of ozone depletion in terms of UV carcinogenesis is not only increasing total amount of UV but also increasing biologically highly reactive spectrum of UVB range.

UVB-susceptibility is dictated by alleles at two, independent genetic loci, that can influence transcriptional and translational activity of the TNF-__gene. A similar findings of UV induced immune suppression has been observed with human volunteers as well. UV exposure suppresses the induction of a contact hypersensitivity (CHS) reaction in a 40-50 % of normal human volunteers, however, in almost 100 % of biopsy-proven skin cancer patients. This finding suggests that immune suppression generated by UV is one of the factors for developing skin cancers. Immunological modulation by UVB is well studied in animal models, however, UVA effect on immunological response remains to be an answered question.

Another relevance of UV induced immune suppression is concerning infection, especially viral, fungus and mycobactirium infection for which human body defend by cellular immunity. However, there are not accurate data of human beings on this matter and epidemiological studies should be needed.

UV-Induced Immunosuppression and Stratospheric Ozone Depletion

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A body of experimental evidence has resulted in a model for experimental skin cancer formation in which UVB initiates two separate events, the neoplastic transformation of skin cells and a well-described selective down-regulation of immune function. There is considerable evidence from experimental systems that this form of immunosuppression is a critical step in UV carcinogenesis, preventing immunologic destruction of highly antigenic UV-induced skin cancers. UVB-induced immune suppression may be a fundamental regulatory mechanism, controlling interaction between mammals and potentially deleterious environmental radiation. This mechanism may have evolved to protect against autoimmune attack on sunlight damaged skin with the inadvertent consequence of preventing immune attack on UV-induced skin cancers.

In a number of experimental systems it has further been demonstrated that UV irradiation of a host can alter the pathogenesis of disease and the immune response to a variety of infectious agents including malaria and Leishmania parasites, influenza and herpes viruses, and Mycobacteria. These findings further raise the question of whether the immunosuppression caused by UV irradiation alters vaccine efficacy. A role for UV immunosuppression in some forms of autoimmune disease has been postulated.

In humans, UV radiation also initiates immunosuppression, similar to that described in animals. The UV dose-responses for immunosuppression are similar in mouse and in man and many of the mediators of UV immunosuppression in mouse models are formed in human skin suggesting that the mouse is a good model for man. There have been however few experimental or epidemiological investigations in humans on the role of UV immunosuppression in human disease. This topic urgently needs investigation. Genetically determined differences in susceptibility to UV immunosuppression have been described in the mouse and QTLs have been mapped. It has been postulated that genetic differences in susceptibility to UV immunosuppression may be a risk factor for skin cancer in humans. Although differences in susceptibility to UV-induced immunosuppression have been described in humans it has not been proven as yet that these are genetically determined.

Mechanistically, UV irradiation initiates a peripheral active tolerance of cell-mediated immunity, transferable with T lymphocytes, to a wide variety of antigens usually, though not always, introduced via the skin. UV immunosuppression is dose and wavelength dependent and is initiated by wavelengths in the UVB (290-320nm) spectrum. Contact and delayed-type hypersensitivity responses to a wide variety of antigens delivered via the skin of a UVB treated mouse, either at the UVB irradiated site or at an unirradiated site are decreased. The effect of UVB appears to be mediated via direct and indirect UVB alterations to dendritic antigen presenting cells, resulting in preferential down regulation of Th1 responses and with the formation of antigen specific “suppressor” T lymphocytes. These appear to function through CTLA-4 engagement and IL-10 release and may correspond to the regulatory T cells described in other systems. UV initiates immunosuppression apparently by multiple mechanisms. UV causes isomerization of a photoreceptor molecule urocanic acid (UCA) in the skin, the cis isomer of which is immunosuppressive. Neuropeptides released in the skin by UV radiation have also been shown to be immunosuppressive. Direct DNA damage by UV irradiation appears to elicit immunosuppression by damage to epidermal Langerhans cells and/or by release of immunosuppressive cytokines.

A detailed action spectrum (wavelength dependence) for UV-induced immunosuppression of contact hypersensitivity derived in a mouse model and a radiative transfer model to describe sunlight irradiance have been used to predict levels of UV-induced immunosuppression as a function of latitude and of increases in UV radiation predicted to result from stratospheric ozone depletion. Values for the biologically effective irradiance (BEI_{ims}) for 50% immunosuppression of contact hypersensitivity in sunlight varied as a function of latitude and of season from 0.87×10^{-2} W/m^2 at 60N in January to 33.2×10^{-2} W/m$^{2\ at}$ 20S in July predicting that for a mouse, 50% suppression of CHS could be achieved in less than 30 minutes of noontime exposure in summer in Rockville, MD. The radiation amplification factors calculated to result from ozone depletion scenarios from 5 to 20% were between 0.6 and 1% for each 1% decrease in stratospheric ozone. Since these calculations were made, experimental evidence has been

produced that UVA (320-400nm) can inhibit the immunosuppression initiated by UVB, suggesting that UVA/UVB ratios may be critical for this effect. If this is the case for humans, then the increases in immunosuppression due to stratospheric ozone depletion may be quite different. In order to calculate accurately risk factors from sunlight exposure as a function of latitude and season, therefore, an action spectrum for this UVA effect is needed.

Appendix C: Opening Remarks by Dr. Kirschstein and Dr. Ono

Opening Remarks

Dr. Ruth Kirschstein
Acting Director of the National Institutes of Health

Good morning and welcome. The National Institutes of Health, the National Institute of Environmental Health Sciences and the National Science Foundation are very pleased to host the 8th US-Japan Workshop on the Impacts of Global Change on Human Health. This is a very timely workshop because both the Intergovernmental Panel on Climate Change (IPCC) and the US Global Change Research Program (USGCRP) are in the final phases of providing extensive assessments, as to the impacts of global change on human health and on the environment over the next 50-100 years. In addition, the USGCRP is in the process of developing a research agenda related to global change for the next 10 years.

We are very pleased to welcome our Japanese colleagues to this workshop and to the NIH campus. In the delegation from Japan, we want to note particularly the presence of Dr. Gen Ohi, Director General of the National Institute for Environmental Studies in Tsukuba, Ibaraki Prefecture, and Dr. Michinori Kabuto, the co-convenor of this Workshop from Japan who is Director of the Regional Environment Division at the NIES. The co-convener for the United States is Dr. Warren Piver from NIEHS. The workshop has been organized into two very broad areas. For the session on greater exposures to higher temperatures and concentrations of air pollutants, the chairs are Dr. Yasushi Honda from the University of Tsukuba and Dr. Frank Speizer from Harvard Medical School. For the session on depletion of stratospheric ozone and greater exposures to shorter wavelength UV radiation, the chairs are Dr. Sumihiro Akiba from Kagoshima University Faculty of Medicine and Dr. Margaret Kripke from the M.D. Anderson Cancer Center, University of Texas.

This is a very unique workshop because you, the participants, will be developing collaborative research activities between the United States and Japan for events that have not yet occurred. The global change scenarios that have been developed by the IPCC project an increase in surface temperatures of 2-5°C and a sea level rise of 0.5 to 1 meter in the next 50 to 100 years. Temperature changes of this magnitude appear to be linked to increasing atmospheric concentrations of CO_2. A primary source of increasing CO_2 concentrations is the combustion of fossil fuels. Therefore, along with greater and more long lasting exposures to higher temperatures, especially for people who live in urban areas, there could also be greater and more long lasting exposures to concentrations of air pollutants. Therefore a possible scenario for the impacts of global change on human health is the finding of an increase in morbidity and mortality for those diseases related to exposures to both higher temperatures and concentrations of air pollutants.

At the present time, depletion of stratospheric ozone is occurring primarily over the polar regions on our planet. In the next 25 to 50 years, however, there could be significant depletion of stratospheric ozone over temperate and equatorial latitudes where most of the world's populations live. In these latitudes, depletion of stratospheric ozone may result in greater exposures to shorter wavelength UV radiation and may result in increases in rates of skin cancers, ocular diseases and diseases associated with compromised cutaneous and systemic immune systems.

Finally, these are changes that could affect our grandchildren and our great grandchildren. The challenges before you are very great because you must use the information and methods of analysis that you have presently, and project what the impacts of global change on human health may be in the future. In this regard, it is significant that our two great nations are combining our best efforts to examine the effects of global change. You will help to identify and develop the fundamental research and knowledge bases that will be necessary to estimate the impacts of these changes on human health around the world. Because of its unique mission on environmental health research, the NIEHS has provided important leadership for many NIH Institutes, notably NCI, NEI, NIAID, NHLBI and NIMH, to contribute their considerable research resources for addressing human health issues associated with global change. From this base, the NIH is reaching out to other Federal agencies. Twelve new interdisciplinary research projects have just been funded under a joint initiative between NIH, the National Science Foundation, and other Federal

agencies to study how large-scale environmental events—such as habitat destruction, biological invasion, and pollution—alter the risks of emergence of viral, parasitic, and bacterial diseases in humans and other animals. We will continue to work in the coming months to develop the multi-disciplinary and multi-agency research programs that will be necessary to estimate and assess the impacts of global change on human health now and in the future.

Ladies and gentlemen, I salute you for taking on this enormous challenge. You have my best wishes for a successful workshop.

Opening Remarks

Dr. Gen OHI
Director of the National Institute for Environmental Studies

Good morning, everyone. First of all, I would like to thank the host organizers of this Workshop for providing the stage to exchange information and thoughts of distinguished scholars in both countries.

Since Dr Kirschstein has just covered so adequately the expected research activities expanding over 10, 50 to 100 years from now, I may be forgiven for searching an uncovered domain—the past, in particular the last 150 years.

It was from 1852 to 1853 when Commodore Matthew C Perry navigated, leaving Norfolk, Virginia, via the Atlantic and the Indian Ocean, and arrived at the Bay of Tokyo, then called Edo. It took him 7 odd months. Only 2 decades afterwards Dr. William Smith Clark, was invited from Massachusetts Agricultural College to assume the first presidency of Sapporo Agricultural College, which later became Hokkaido University. It took him 5 weeks to traverse the North American Continent and the Pacific before reaching Yokohama. At that time Hokkaido, the northern island of Japanese Archipelago, was mostly covered with pristine forests and people were soley concerned with how to exploit and harness the vast, seemingly endless space.

A little more than a century has passed since then. In the meantime, we have witnessed a variety of dramatic changes: population explosion, global pollution, global warming, to name a few. Perhaps a most radical change is the shrinkage of our habitat relative to our activities. Needless to say, it takes only a little more than half a day to fly from Japan to the Eastern Seaboard of US. In other words, the size of our habitat has shrank to less than one hundredth to five hundredth compared to only 150 years ago. The trouble with the humans is that their majority continues to live, consume and discard with the perception of space, which was formed in the preceding centuries of far less human activities and densities.

However, it seems to me that there is a growing realization among the students of environmental sciences, which may help break the false perception of space we still carry, that is the realization that one phenomenon or event is necessarily related to all other phenomena or events. This principle of interrelatedness or, in Sanskrit, pratitya-samutpada was already known 2500 years ago in India. For instance, once the great China Sea separating mainland China from Japan appeared vast, posing a rather un-sunmountable barrier. We can now observe that, at the time of a great flood of Yangtze River, its silts are carried away as far as North Korean or Russian coasts facing the Japan Sea and on the Pacific side, as far as Osaka or even Tokyo. Perhaps the best example is the effects of CO2 we emit. We know that in global warming a cause-result relationship is not linear or mono-directional but pan-directional: perpetrators are at once victims and victims are perpetrators.

Our current situation could be likened to a group of 10 people destined to live in a 10m by 10m room. Or, in Japanese expression, 10 people on 10 tatami-matresses. They will have to live in a highly concerted fashion without causing conflicts, without polluting the floor, if they wish to keep the room habitable for the next generation inhabitants. Actually such life style can be found among Zen-buddhits in Asia. I believe this situation will give us another rationale to invigorate our collaborative work to be conducted by the environmental scientists of both nations gathering now in this auditorium.

Thank you.

Appendix D: List of Acronyms

AMeDAS	Automated Meteorological Data Acquisition System
COPD	Chronic Obstructive Pulmonary Disease
CPC	Climate Prediction Center
EPA	Environmental Protection Agency (U.S.)
GHCN	Global Historical Climatology Network
GIS	Geographic Information System
HPV	Human Papillomaviurs
HTLV-I	Human T-lymphotropic Virus, type 1
IPCC	Intergovernmental Panel on Climate Change
JEA	Japan Environmental Agency
NASA	National Aeronautics and Space Agency (U.S.)
NCI	National Cancer Institute (U.S.)
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NIAID	National Institute of Allergy and Infectious Diseases
NIEHS	National Institute for Environmental Health Science (U.S.)
NIES	National Institute of Environmental Studies (Japan)
NIH	National Institutes of Health (U.S.)
NIMH	National Institute of Mental Health
NOAA	National Oceans and Atmospheric Administration (U.S.)
NSF	National Science Foundation (U.S.)
NCDC	National Climate Data Center (U.S.)
PAH	polyaromatic hydrocarbons
SHADOZ	Southern Hemisphere Additional OZonesondes
STA	Science and Technology Agency (Japan)
TOMS	Total Ozone Mapping Spectrometer
USDA	U.S. Department of Agriculture
USGCRP	U.S. Global Change Research Program
UV	Ultraviolet
VOC	volatile organic compounds

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